Exhibit 2

CT Corporation

Service of Process Transmittal

12/12/2018
CT Log Number 534568577

TO: Carol Purcell
Endo Pharmaceuticals Inc.
1400 Atwater Dr
Malvern, PA 19355-8701

RE: **Process Served in Texas**

FOR: Endo Pharmaceuticals Inc. (Domestic State: DE)

ENCLOSED ARE COPIES OF LEGAL PROCESS RECEIVED BY THE STATUTORY AGENT OF THE ABOVE COMPANY AS FOLLOWS:

TITLE OF ACTION:	COUNTY OF NEWTON, Pltf. vs. PURDUE PHARMA L.P., et al., Dfts. // To: Endo Pharmaceuticals Inc
DOCUMENT(S) SERVED:	Citation, Return, Petition, Attachment(s), Exhibit(s)
COURT/AGENCY:	None Specified Case # 14467
NATURE OF ACTION:	Product Liability Litigation - Drug Litigation - opioids
ON WHOM PROCESS WAS SERVED:	C T Corporation System, Dallas, TX
DATE AND HOUR OF SERVICE:	By Process Server on 12/12/2018 at 15:55
JURISDICTION SERVED :	Texas
APPEARANCE OR ANSWER DUE:	Within 20 days after service
ATTORNEY(S) / SENDER(S):	Courtney Tracy Ponthier 110 Court Street Room 121 P.O. Drawer 36 Newton, TX 75966 409-379-8600
ACTION ITEMS:	CT has retained the current log, Retain Date: 12/14/2018, Expected Purge Date: 12/19/2018 Image SOP Email Notification, Jobina Jones-McDonnell jones.jobina@endo.com Email Notification, Helen Howlett howlett.helen@endo.com Email Notification, Marian Gustafson marian.gustafson@parpharm.com Email Notification, Carolyn Hazard hazard.carrie@endo.com Email Notification, Par Notice Dept Par.noticeDept@parpharm.com Email Notification, Carol Purcell Purcell.Carol@endo.com Email Notification, Stephanie Stidham stidham.stephanie@endo.com

CT Corporation

Service of Process Transmittal

12/12/2018
CT Log Number 534568577

TO: Carol Purcell
Endo Pharmaceuticals Inc.
1400 Atwater Dr
Malvern, PA 19355-8701

RE: **Process Served in Texas**

FOR: Endo Pharmaceuticals Inc. (Domestic State: DE)

Email Notification, Sandra Dilorio Dilorio.Sandra@endo.com

SIGNED: C T Corporation System
ADDRESS: 1999 Bryan Street
Suite 900
Dallas, TX 75201
TELEPHONE: 214-932-3601

12-8-18

COPY

CIVIL CITATION

CLERK OF THE COURT
BREE ALLEN
PO BOX 535
NEWTON, TX 75966

ATTORNEY FOR PETITIONER
JEFFREY SIMON
1201 ELM STREET, STE 3400
DALLAS, TX 75270

THE STATE OF TEXAS

NOTICE TO DEFENDANT: "You have been sued. You may employ an attorney. If you or your attorney do not file a written answer with the clerk who issued this citation by 10:00 a.m. on the Monday next following the expiration of twenty days after you were served this citation and petition, a default judgment may be taken against you."

TO: ENDO PHARMACEUTICALS, INC. c/o CT Corporation System, 1999 Bryan Street, Ste900 Dallas, Tx 75201 or wherever he/she may be found.

GREETINGS: You are commanded to appear by filing a written answer to the Plaintiff's Original Petition at or before 10:00 o'clock a.m. of the Monday next after the expiration of 20 days after the date of service hereof, before the District Court of Newton Texas, at the Courthouse in Newton, Texas.

Said Petition was filed on **DECEMBER 7, 2018**

The file number of said suit being **14467.**

The style of the case is:

COUNTY OF NEWTON
Plaintiff

VS.

PURDUE PHARMA L.P. et al.
Defendant

A copy of Plaintiff's ORIGINAL PETITION accompanies this citation.
Issued on DECEMBER 10, 2018

GIVEN UNDER MY HAND AND SEAL OF SAID COURT, at office in Newton, Texas, on DECEMBER 10, 2018.

DISTRICT COURT NEWTON COUNTY, TEXAS

Bree Allen

Bree Allen, District Clerk
District Court
Newton County, Texas

By: Dayeon Woods, Deputy

OFFICER'S RETURN

Came to hand on the _____ day of _____, 20____, at _____, o'clock ____.m., and executed in _____ County, Texas by delivering to each of the within named defendants in person, a true copy of this Citation with the date of delivery endorsed thereon, together with the accompanying copy of the plaintiff's petition, at the following times and places, to-wit:

Name	Date/Time	Place, Course and Distance from Courthouse
_____	_____	_____

And not executed as to the defendant(s), _____

The diligence used in finding said defendant(s) being:

_____

and the cause or failure to execute this process is:

_____

and the information received as to the whereabouts of said defendant(s) being:

_____

FEES:

Serving Petition and Copy $_____

Total $_____

_____, Officer

_____, County, Texas

By:_____, Deputy

E-Filed for Record
12/7/2018 4:03 PM
Newton County District Clerk , TX
By: Vanessa Woods

14467

CAUSE NO. _____

COUNTY OF NEWTON,	§	**IN THE DISTRICT COURT**
	§	
Plaintiff,	§	
	§	
vs.	§	**_____ JUDICIAL DISTRICT**
	§	
PURDUE PHARMA L.P.;	§	
PURDUE PHARMA INC.;	§	
THE PURDUE FREDERICK COMPANY;	§	
JOHNSON & JOHNSON;	§	**NEWTON COUNTY, TEXAS**
JANSSEN PHARMACEUTICALS, INC.;	§	
ORTHO-MCNEIL-JANSSEN	§	
PHARMACEUTICALS, INC. n/k/a	§	
JANSSEN PHARMACEUTICALS, INC.;	§	
JANSSEN PHARMACEUTICA INC. n/k/a	§	
JANSSEN PHARMACEUTICALS, INC.;	§	
ENDO HEALTH SOLUTIONS INC.;	§	
ENDO PHARMACEUTICALS, INC.; and	§	
DOES 1 – 100, INCLUSIVE,	§	
	§	
Defendants.	§	

PLAINTIFF'S ORIGINAL PETITION AND JURY DEMAND

TO THE HONORABLE JUDGE OF SAID COURT:

NOW COMES Plaintiff, the County of Newton, Texas (hereinafter "Newton County" or "County"), by and through the undersigned attorneys, on behalf of the District Attorney for Newton County, against Defendants Purdue Pharma L.P., Purdue Pharma Inc., The Purdue Frederick Company, Johnson & Johnson, Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica Inc. n/k/a Janssen Pharmaceuticals, Inc., Ortho-McNeil-Janssen Pharmaceuticals, Inc. n/k/a Janssen Pharmaceuticals, Inc., Endo Health Solutions Inc., Endo Pharmaceuticals, Inc., and Does 1 – 100, alleges as follows:

I. INTRODUCTION

1. The United States is in the midst of an opioid epidemic caused by Defendants' fraudulent marketing, sales, and distribution of prescription opioids ("opioids") that has resulted in addiction, criminal activity, and loss of life.[1] Americans "consume 85% of all the opioids in the world" and are "the most medicated country in the world . . . ."[2] The opioid crisis has been described as "the AIDS epidemic of our generation, but even worse."[3] On October 26, 2017, President Donald Trump "declared a nationwide public health emergency to combat the opioid crisis."[4]

2. In 1997, each person in the United States, on average, consumed 96 mg morphine equivalents. In 2010 that number increased to 710 mg per person.[5] This amount has been estimated as the equivalent to 7.1 kg of opioids per 10,000 people – or enough to supply each American with 5 mg of hydrocodone every 6 hours for 45 days.[6]

3. It's no surprise that in 2016 alone, health care providers wrote more than 289 million prescriptions for opioids, enough for *every adult in the United States* to have more than one bottle of pills.[7]

4. Unfortunately, using opioids too often leads to addiction and overdose from opioids. It was estimated as early as 2001 that up to 40% of chronic pain patients were addicted to

---

[1] L. Manchikanti, *Opioid Epidemic in the United States*, Pain Physician, Jul. 2012, at 1, www.painphysicianjournal.org, attached hereto as Exhibit A.
[2] David Wright, *Christie on Opioids: "This is the AIDS Epidemic of Our Generation, but even Worse,"* CNN, Oct. 27, 2017, *available at* http://www.cnn.com/2017/10/27/politics/chris-christie-opioid-commission-aids-cnntv/index.html; Manchikanti, Ex. A, at 16 ("Gram for gram, people in the United States consume more narcotic medication than any other nation worldwide.").
[3] Wright, *supra.*
[4] Dan Merica, *What Trump's Opioid Announcement Means – and Doesn't Mean*, CNN, Oct. 26, 2017, *available at* http://www.cnn.com/2017/10/26/politics/national-health-emergency-national-disaster/index.html.
[5] Manchikanti, Ex. A, at 14.
[6] *Id.*
[7] *Prevalence of Opioid Misuse*, BupPractice, Sept. 7, 2017, *available at* https://www.buppractice.com/node/15576.

opioid pain medication.[8] Almost 2 million Americans were addicted to opioids in 2014.[9] To put the opioid crisis in perspective, the statistics demonstrate:

- Roughly 21 to 29 percent of patients prescribed opioids for chronic pain misuse them;
- Between 8 and 12 percent develop an opioid use disorder; and
- About 80 percent of people who use heroin first misused prescription opioids.[10]

5. In 2014, more people died from drug overdoses than in any other year. Currently more than 115 Americans die every day after overdosing on opioids.[11] The Texas Legislature has found "that deaths resulting from the use of opioids and other controlled substances constitute a public health crisis."[12]

6. In fact, accidental drug overdose deaths, of which reportedly at least two-thirds are opioid overdoses, are the leading cause of death for Americans under the age of 50. And these accidental opioid drug overdose deaths exceed the number of deaths caused by cars or guns. A report from the CDC found that from July 2016 to September 2017, emergency visits due to suspected opioid overdoses continued to climb approximately 30% across the nation.[13] The increase was seen in adults of all age groups and in men and women in all geographic areas.[14]

7. Over the next decade, the average number of deaths due to opioids is expected to be 500,000.[15] Proof that the opioid epidemic is far from slowing is the latest statistic that

---

[8] *Prescription Drugs: Abuse and Addiction*, National Institute of Drug Abuse (NIH Publication), Jul. 2001, at 13.
[9] *National Survey on Drug Use and Health*, Substance Abuse and Mental Health Services Administration, 2014.
[10] *Opioid Overdose Crisis*, National Institute on Drug Abuse, Jan. 2018, *available at* https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis.
[11] *Id.*
[12] Tex. Att'y Gen. Op. No. KP-0168 (2017), *citing* Act of May 26, 2017, 85th Leg., R.S., ch. 534, § 3, 2017 Tex. Sess. Law Serv. 1467, 1468.
[13] Jacqueline Howard, *ER Visits for Opioid Overdose up 30%, CDC Study Finds*, CNN, Mar. 6, 2018.
[14] *Id.*
[15] Max Blau, *STAT forecast: Opioids Could Kill Nearly 500,000 American in the next Decade*, STAT, June 27, 2017, *available at* https://www.statnews.com/2017/06/27/opioid-deaths-forecast/; *see also* Wes Rapaport, *Advocates for Painkiller Advocates Wants Society to Meet Them Halfway*, Big Country, Feb. 18, 2018 (stating the

approximately 72,000 Americans died from drug overdoses last year in 2017.[16] This increase is due to a growing number of Americans using opioids and the opioids themselves are becoming more deadly.[17] The economic burden caused by opioid abuse in the United States is at least $78.5 billion,[18] including lost productivity and increased social services, health insurance costs, increased criminal justice presence and strain on judicial resources, and substance abuse treatment and rehabilitation.[19] In 2015, Texas "had the second highest total healthcare costs from opioid abuse in the nation ($1.96 billion) . . . ."[20]

8. This epidemic did not occur by chance. Defendants manufacture, market, distribute, and sell prescription opioids, including, but not limited to, brand-name drugs like OxyContin, Opana, Percocet, Percodan, Duragesic, Ultram, Ultracet, and generics like oxycodone, oxymorphone, hydromorphone, hydrocodone, fentanyl, and tramadol, which are powerful narcotics.

9. Historically, opioids were considered too addictive and debilitating for treating non-cancer chronic pain,[21] such as back pain, migraines, and arthritis, and were used only to treat short-term acute pain or for palliative or end-of-life care.

10. By the late 1990s or early 2000s, however, each Defendant began a marketing scheme to persuade doctors and patients that opioids were not addictive and should be used

---

number of opioid overdose deaths is going to go up for at least several more years and explaining how Operation Naloxone has administered more than $1 million of the powerful antidote).

[16] Margot Sanger-Katz, *Bleak New Estimates in Drug Epidemic: A Record 72,000 Overdose Deaths in 2017*, The New York Times, Aug. 15, 2018, https://www.nytimes.com/2018/08/15/upshot/opioids-overdose-deaths-rising-fentanyl.html (representing a 9.5 percent increase from 2016).

[17] *Id.*

[18] *CDC Foundation's New Business Pulse Focuses on Opioid Overdose Epidemic*, Centers for Disease Control and Prevention, Mar. 15, 2017, *available at* https://www.cdc.gov/media/releases/2017/a0315-business-pulse-opioids.html.

[19] *Opioid Overdose Crisis, supra.*

[20] Kerry Craig, *Opioid Addiction Results in one Woman's Daily Struggle*, Sulphur Springs News-Telegram, Oct. 7, 2017, *available at* https://www.ssnewstelegram.com/news/opioid-addiction-results-in-one-woman-s-daily-struggle/article_bded4eoa-ab80-11e7-a252-d3f304e26628.html.

[21] "Chronic pain" means non-cancer pain lasting three months or longer.

ubiquitously and perpetually to treat moderate, non-cancer chronic pain.[22] Defendants' efforts to "increase opioid use" and their campaign emphasizing "the alleged undertreatment of pain continue to be significant factors of the [opioid] escalation."[23] Defendants reassured the medical community that opioids were not addictive and doctors prescribed them at a higher rate.[24] Consequently, the National Institute of Drug Abuse attributes the opioid crises to Defendants' successful marketing campaign.[25] Each Defendant spent, and continues to spend large sums of money to promote the benefits of opioids for non-cancer moderate pain while trivializing or even denying their risks.

11. The Defendants' promotional messages deviated substantially from any approved labeling of the drugs and caused prescribing physicians and consuming patients to underappreciate the health risks, and to overestimate the benefits of opioids.

12. Contrary to the language of their drugs' labels, Defendants falsely and misleadingly, in their marketing: (1) downplayed the serious risk of addiction; (2) promoted and exaggerated the concept of "pseudoaddiction" thereby advocating that the signs of addiction should be treated with more opioids; (3) exaggerated the effectiveness of screening tools in preventing addiction; (4) claimed that opioid dependence and withdrawal are easily managed; (5) denied the risks of higher opioid dosages; and (6) exaggerated the effectiveness of "abuse-deterrent" opioid formulations to prevent abuse and addiction.

---

[22] *See e.g., Opioid Overdose Crisis*, National Institute on Drug Abuse, Jan. 2018, *available at* https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis (explaining the greater rate of prescribing opioids due to misinformation to physicians, which led to a diversion and misuse of opioids before anyone knew opioids were highly addictive).
[23] Manchikanti, Ex. A, at 1.
[24] CDC/NCHS, *National Vital Statistics System, Mortality*, CDC Wonder, Atlanta, Ga: US Department of Health and Human Services, 2017, *available at https://wonder.cdc.gov.*
[25] *See id.*

13. Defendants disseminated these falsehoods through ads, sales representatives, and/or hand-picked physicians who supported Defendants' message. Sales representatives, working at Defendants' behest, promoted highly addictive opioids through souvenirs and toys including, but not limited to, opioid brand-bearing stuffed plush toys, dolls, coffee cups, fanny packs, water bottles, notepads, pens, refrigerator magnets, clocks, letter openers, rulers, daytime planners, bags, puzzles, posters, hand-held calculators, clipboards, highlighters, flashlights, key chains, clothing, reflex mallets, and mock-ups of the United States Constitution.

14. Defendants also used third parties they controlled by: (a) funding, assisting, encouraging, and directing doctors, known as "key opinion leaders" ("KOLs") and (b) funding, assisting, directing, and encouraging seemingly neutral and credible professional societies and patient advocacy groups (referred to hereinafter as "Front Groups").

15. Defendants worked with KOLs and Front Groups to taint the sources that doctors and patients relied on for ostensibly "neutral" guidance, such as treatment guidelines, Continuing Medical Education ("CME") programs, medical conferences and seminars, and scientific articles. Through their individual and concerted efforts, Defendants convinced doctors that instead of being addictive and unsafe for long-term use in most circumstances, opioids were *required* in the compassionate treatment of chronic pain, which Defendants termed an epidemic in America.

16. Defendants' aggressive marketing of opioids for chronic pain is "based on unsound science and blatant misinformation, and accompanied by the dangerous assumptions that opioids are highly effective and safe, and devoid of adverse events when prescribed by physicians."[26] Nevertheless, Defendants' marketing was effective and, by 2011 there were 136.7 million prescriptions for hydrocodone alone, with all opioids exceeding 238 million.[27] Data demonstrates

[26] Manchikanti, Ex. A, at 1-4.
[27] *Id.*

that "[o]ver 90% of patients received opioids for chronic pain management."[28]

17. Essentially each Defendant ignored science and consumer health for profits. Defendants' efforts were so successful that opioids are now the most prescribed class of drugs generating $11 billion in revenue for drug companies in 2014 alone. Sales for Purdue's OxyContin grew from $48 million in 1996 to $1.1 billion in 2000 after it successfully and aggressively marketed and promoted its opioid.[29] In fact, OxyContin was a "leading drug of abuse" by 2004 through its availability.[30] Even after Purdue reached a $600 million federal settlement in 2007, the settlement failed to impact what is a "$13-billion-a-year opioid industry."[31]

18. As a direct and foreseeable consequence of Defendants' misrepresentations and misleading marketing campaign to Newton County physicians and residents regarding the safety and efficacy of using opioids for chronic non-cancer pain that resulted in an oversupply of opioids, Newton County has spent and continues to spend large sums of money combatting the public health crisis.

19. The money Newton County has spent comes directly from its taxpayers. These taxpayers include Newton County physicians, who passed on Defendants' misleading safety and efficacy information and prescribed more opioids to taxpaying residents in Newton County. These taxpayers also included Newton County residents who either suffered the addictive effects of consuming opioids or overdosed using Defendants' opioids that had been over-prescribed and over-supplied to Newton County as intended by Defendants herein. Thus, this group of Newton County residents has suffered not only injury to property, but also bodily injury, as a result of

---

[28] Manchikanti, Ex. A, at 1-4.
[29] Art Van Zee, M.D., *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99 Am. J. Public Health 221, Feb. 2009, at 1, attached hereto as Exhibit B.
[30] Zee, *supra*.
[31] Rebecca L. Haffajee, J.D., Ph.D., M.P.H. and Michelle M. Mello, J.D., Ph.D., *Drug Companies' Liability for the Opioid Epidemic*, N. Engl. J. Med., Dec. 14, 2017, at 2305.

Defendants' misconduct in the false promotion and/or over-supply of prescription opioids.

20. Newton County has spent and continues to spend large sums of money combatting the opioid crisis created by Defendants' negligent and fraudulent marketing campaign. Across the country, including Texas, increased opioid prescribing has caused and continues to cause an increase in overdoses and death. Defendants tracked the CDC data and knew that the more they promoted opioid prescribing and distributed more opioids that non-therapeutic outcomes, such as overdose, addiction, and criminality would occur. By 2010, enough opioids had been sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month.[32] The increased use of opioids has contributed to the increased rate of overdose deaths and nonmedical use with the varying rates of sales in each state impacting the outcomes in each state.[33] "Given that 3% of physicians accounted for 62% of the [opioids] prescribed in one study, the proliferation of high-volume prescribers can have a large impact on state use of [opioids] and overdose death rates."[34] Not surprisingly, "[l]arge increases in overdoses involving the types of drugs sold by illegitimate pain clinics (i.e., 'pill mills') have been reported in Florida and Texas."[35] For example, thousands of prescriptions were written for opioids in Newton County from 2012 – 2016, [36] and in 2016, there were approximately 24 – 25.9 deaths per 100,000 people reported from drug overdoses.[37] A substantial number of those overdose deaths were a result, in whole or in part, of opioid ingestion. Defendants' marketing misconduct, as well as Defendants' efforts to sell more prescription opioids than can be consumed therapeutically, were natural and foreseeable causes of

---

[32] Center for Disease Control, *Vital Signs: Overdoses of Prescription Opioid Pain Relievers – United States, 1999-2008*, Morbidity and Mortality Weekly Report (MMWR), Nov. 4, 2011.
[33] *Id.*
[34] *Id.*
[35] *Id.*
[36] https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html; https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality.
[37] https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality.

overdose deaths and injuries in Newton County.

21. As a direct and foreseeable consequence of Defendants' conduct described regarding prescription opioids, Newton County has committed and continues to commit resources to provide and pay additional health care, law enforcement, social services, public assistance, pharmaceutical care and other services necessary for its residents.

II. RULE 47 STATEMENT OF MONETARY RELIEF SOUGHT

22. Per Rule 47 of the Texas Rules of Civil Procedure, the County states that although the full measure of its damages is still being calculated, its damages caused by Defendants' acts and omissions exceed $1,000,000 but are believed to be less than $100,000,000. Accordingly, at this time in the litigation, Newton County states that it is seeking monetary relief for an amount greater than $1,000,000 and less than $100,000,000, the rightful and just amount to be determined by the jury.

III. STANDING

23. Newton County has standing to bring this lawsuit because it has suffered an injury-in-fact caused by Defendants' misconduct, and that harm can be redressed through this action. Having decided that it was necessary to pursue these claims to protect the County's interests, the County hired outside counsel to handle the litigation.[38] The contract governing the County's representation in this litigation was approved by the Texas Comptroller of Public Accounts pursuant to Tex. Gov't Code § 403.0305.[39]

24. Defendants' misconduct has placed an unreasonable burden on Newton County's resources and ability to provide the public services and employee benefits it is obligated to and/or

[38] *See* Resolution for approval of bringing suit on behalf of Newton County, Texas, vs. various drug manufacturers, developers, suppliers and others of a class of pharmaceutical class of drugs commonly referred to as opioids and approval of Professional Services Agreement for Special Counsel attached hereto as Exhibit G and Executed and Approved Retention Agreement attached hereto as Exhibit H.
[39] *Id.*

has authority to provide to its residents and employees. Newton County has the statutory duty and/or authority to provide public safety and health services, including, but not limited to, the following:

- Supporting paupers;[40]
- Providing county jails;[41]
- Providing health care in county jails;[42]
- Providing fire protection;[43]
- Enforcing drug laws;[44]
- Contracting with drug centers;[45]
- Commissioning drug education and counseling programs;[46] and
- Paying county and precinct officers and employee compensation, office and travel expenses, and any other allowances.[47]

25. Defendants' misconduct – including Defendants' calculated marketing campaign of misinformation to physicians and patients – caused the damages to the County. They misled physicians into overprescribing opioids, which directly created the need for dramatically increased public services. The County relied on these misrepresentations in paying for its employees' healthcare costs causing the County to incur increased healthcare costs for its own employees.

26. The harm caused by Defendants' misconduct can be redressed by the Court in this action. Defendants should be enjoined from continuing to manufacture, distribute, and sell opioids in Newton County without educating physicians and patients about the actual risks and benefits of

[40] Tex. Local Gov't Code § 81.027.
[41] *Id.* at § 351.001.
[42] *Id.* at § 351.045.
[43] *Id.* at § 352.001.
[44] *Id.* at § 370.003.
[45] Tex. Health & Safety Code at § 464.032.
[46] *Id.* at § 465.001
[47] Tex. Local Gov't Code § 152.011.

its drugs. Furthermore, Defendants should compensate Newton County for the funds it has expended and continues to expend for medical insurance claims for opioids that were not medically necessary, as well as increased costs of social services, health systems, law enforcement, the judicial system, and treatment facilities.

IV. VENUE AND JURISDICTION

27. Venue is proper in Newton County because all or a substantial part of the events or omissions giving rise to this claim occurred in Newton County. TEX. CIV. PRAC. & REM. CODE §15.002(a)(2). This Court has subject-matter jurisdiction over this matter because Plaintiff's damages are in excess of the minimal jurisdictional limits of this Court. TEX. GOVT. CODE §24.007(b).

28. This Court has specific jurisdiction over all Defendants as their activities were directed toward Texas, and injuries complained of herein resulted from their activities. *Guardian Royal Exchange Assur., Ltd. v. English China Clays, P.L.C.*, 815 S.W.2d 223, 227 (Tex. 1991). Each Defendant has a substantial connection with Texas and the requisite minimum contacts with Texas necessary to constitutionally permit the Court to exercise jurisdiction. *See id.* at 226.

V. PARTIES

A. Plaintiff

29. This action is brought for and on behalf of Newton County, which provides a wide range of services on behalf of its residents, including services for families and children, public health, public assistance, law enforcement, and emergency care.

B. Defendants

30. PURDUE PHARMA L.P. is a limited partnership organized under the laws of Delaware with its principal place of business in Stamford, Connecticut, and has at all times relevant to this litigation conducted business in this State. Said limited partnership is required to maintain

a registered agent for service of process, but it has not designated such an agent. Therefore, said limited partnership may be served with process through the Secretary of State for the State of Texas at its registered agent in Delaware, The Prentice-Hall Corporation System, Inc., 251 Little Falls Drive, Wilmington, DE 19808, pursuant to the Texas Long-Arm Statute, Tex. Civ. Prac. & Rem. Code §§ 17.041-.045. PURDUE PHARMA L.P. is, through its ownership structure, a Texas resident. PURDUE PHARMA INC. is a New York corporation with its principal place of business in Stamford, Connecticut, and has at all times relevant to this litigation conducted business in this State. Said corporation is required to maintain a registered agent for service of process, but it has not designated such an agent. Therefore, said corporation may be served with process through the Secretary of State for the State of Texas at its registered agent in Delaware, Corporation Service Company, 80 State Street, Albany, NY 12207, pursuant to the Texas Long-Arm Statute, Tex. Civ. Prac. & Rem. Code §§ 17.041-.045. THE PURDUE FREDERICK COMPANY is a Delaware corporation with its principal place of business in Stamford, Connecticut, and has at all times relevant to this litigation conducted business in this State. Said corporation is required to maintain a registered agent for service of process, but it has not designated such an agent. Therefore, said corporation may be served with process through the Secretary of State for the State of Texas at its registered agent in Delaware, The Prentice-Hall Corporation System, Inc., 251 Little Falls Drive, Wilmington, DE 19808, pursuant to the Texas Long-Arm Statute, Tex. Civ. Prac. & Rem. Code §§ 17.041-.045 (Purdue Pharma L.P., Purdue Pharma Inc., and The Purdue Frederick Company are hereinafter referred to as "Purdue").

31. Purdue manufactures, promotes, sells, and distributes opioids in the U.S. and Newton County. Purdue's opioid drug, OxyContin, is one of the most addictive and abused prescription drugs in American history. Purdue has promoted opioids throughout the United States

and in Newton County.

32. JANSSEN PHARMACEUTICALS, INC. is a Pennsylvania corporation with its principal place of business in Titusville, New Jersey, and may be served through its registered agent for service of process, CT Corporation System, 1999 Bryan Street, Suite 900, Dallas, TX 75201. JANSSEN PHARMACEUTICALS, INC. is a wholly owned subsidiary of JOHNSON & JOHNSON. JOHNSON & JOHNSON ("J&J") is a New Jersey corporation with its principal place of business in New Brunswick, New Jersey, and has at all times relevant to this litigation conducted business in this State. Said corporation is required to maintain a registered agent for service of process, but it has not designated such an agent. Therefore, said corporation may be served with process through the Secretary of State for the State of Texas at its corporate headquarters, Attention: Legal Department, One Johnson & Johnson Plaza, New Brunswick, NJ 08933, pursuant to the Texas Long-Arm Statute, Tex. Civ. Prac. & Rem. Code §§ 17.041-.045. ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., now known as JANSSEN PHARMACEUTICALS, INC., is a Pennsylvania corporation with its principal place of business in Titusville, New Jersey, and may be served through its registered agent for service of process, CT Corporation System, 1999 Bryan Street, Suite 900, Dallas, TX 75201. JANSSEN PHARMACEUTICA INC., now known as JANSSEN PHARMACEUTICALS, INC., is a Pennsylvania corporation with its principal place of business in Titusville, New Jersey, and may be served through its registered agent for service of process, CT Corporation System, 1999 Bryan Street, Suite 900, Dallas, TX 75201. J&J is the only company that owns more than 10% of Janssen Pharmaceuticals' stock, and corresponds with the FDA regarding Janssen's products. Upon information and belief, J&J controls the sale and development of Janssen Pharmaceuticals' drugs and Janssen's profits inure to J&J's benefit (Janssen Pharmaceuticals, Inc., Ortho-McNeil-Janssen Pharmaceuticals, Inc.,

Janssen Pharmaceutica Inc., and J&J are hereinafter referred to as "Janssen").

33. Janssen manufactures, promotes, sells, and distributes opioids in the U.S. and in Newton County.

34. ENDO HEALTH SOLUTIONS INC. is a Delaware corporation with its principal place of business in Malvern, Pennsylvania, and has at all times relevant to this litigation conducted business in this State. Said corporation is required to maintain a registered agent for service of process, but it has not designated such an agent. Therefore, said corporation may be served with process through the Secretary of State for the State of Texas at its registered agent in Delaware, The Corporation Trust Company, Corporation Trust Center, 1209 Orange St., Wilmington, DE 19801, pursuant to the Texas Long-Arm Statute, Tex. Civ. Prac. & Rem. Code §§ 17.041-.045. ENDO PHARMACEUTICALS, INC., a wholly-owned subsidiary of ENDO HEALTH SOLUTIONS INC., is a Delaware corporation with its principal place of business in Malvern, Pennsylvania, and may be served through its registered agent for service of process, CT Corporation System, 1999 Bryan Street, Suite 900, Dallas, TX 75201 (Endo Health Solutions Inc. and Endo Pharmaceuticals, Inc. are hereinafter referred to as "Endo").

35. Endo develops, markets, and sells opioid drugs in the U.S. and in Newton County. Endo also manufactures and sells generic opioids in the U.S. and Newton County, by itself and through its subsidiary, Qualitest Pharmaceuticals, Inc.

36. The County lacks information sufficient to specifically identify the true names or capacities, whether individual, corporate or otherwise, of Defendants sued herein under the fictitious names DOES 1 through 100 inclusive. The County will amend this Petition to show their true names and capacities if and when they are ascertained. Newton County is informed and believes, and on such information and belief alleges, that each of the Defendants named as a DOE

has engaged in conduct that contributed to cause events and occurrences alleged in this Petition and, as such, shares liability for at least some part of the relief sought herein.

VI. FACTUAL ALLEGATIONS

37. Before the 1990s, generally accepted standards of medical practice dictated that opioids should be used only for short-term acute pain – pain relating to recovery from surgery or for cancer or palliative (end-of-life) care. Using opioids for chronic pain was discouraged or even prohibited because there was a lack of evidence that opioids improved patients' ability to overcome pain and function. Instead the evidence demonstrated that patients developed tolerance to opioids over time, which increased the risk of addiction and other side effects.

38. After the 1990s, Defendants dramatically changed doctors' views regarding opioids through a well-funded deceptive marketing scheme. Defendants were so successful that, according to the National Safety Council, 74% of ***all*** doctors prescribe opioids for chronic back pain and 55% prescribe opioids for dental pain, "neither of which is appropriate in most cases."[48] And 99% of doctors are prescribing tem for longer than the three-day recommended period as recommended by the CDC.[49] Twenty-three percent prescribe at least a month's worth of opioids and evidence shows that just 30 days of usage can cause brain damage.[50]

39. Each Defendant used direct marketing and unbranded advertising (*i.e.*, advertising that promotes opioid use generally but does not name a specific opioid) disseminated by seemingly independent third parties to spread false and deceptive statements about the risks and benefits of long-term opioid use. Defendants advocated the widespread use of opioids for chronic pain even

---

[48] National Safety Council, *NSC Poll: 99% of Doctors Prescribe Highly-Addictive Opioids Longer than CDC Recommends*, 2017 (The NSC was founded in 1913 and chartered by Congress and is a non-profit organization whose mission is to save lives by preventing injuries and deaths at work, in homes, and in the communities through leadership, research, education, and advocacy).
[49] *Id.*
[50] *Id.*

though it contravened the "cardinal principles of medical intervention – that there be compelling evidence of the benefit of a therapy prior to its large-scale use."[51]

A. Defendants Used Multiple Avenues To Disseminate their False and Deceptive Statements about Opioids.

40. Defendants spread their false and deceptive statements by (1) marketing their branded opioids directly to doctors treating patients residing in Newton County and the Newton County patients themselves and (2) deploying so-called unbiased and independent third parties to Newton County.

1. Defendants Spread and Continue to Spread Their False and Deceptive Statements Through Direct Marketing of Their Branded Opioids.

41. Defendants' direct marketing of opioids generally proceeded on two tracks. First, each Defendant conducted advertising campaigns touting the purported benefits of their branded drugs. For example, Purdue spent $200 million promoting and marketing OxyContin in various forms.[52] Defendants spent more than $14 million on medical journal advertising of opioids in 2011, nearly triple what they spent in 2001, including $8.3 million by Purdue, $4.9 million by Janssen, and $1.1 million by Endo.

42. A number of Defendants' branded ads deceptively portrayed the benefits of opioids for chronic pain. For example, Endo distributed and made available on its website, www.opana.com, a pamphlet promoting Opana ER with photographs depicting patients with physically demanding jobs like a construction worker and chef, implying that the drug would provide long-term pain-relief and functional improvement.

43. Purdue also ran a series of ads, called "pain vignettes," for OxyContin in 2012 in medical journals. These ads featured chronic pain patients and recommended OxyContin for each.

---

[51] Manchikanti, Ex. A, at 2.
[52] Zee, Ex. B, at 2.

One ad described a "54-year-old writer with osteoarthritis of the hands" and implied that OxyContin would help the writer work more effectively. Second, each Defendant promoted the use of opioids for chronic pain through "detailers" – sales representatives who visited individual doctors and medical staff in their offices – and small-group speaker programs.

44. Defendants devoted massive resources to direct sales contacts with doctors. In 2014 alone, Defendants spent $154 million on detailing branded opioids to doctors, including $108 million by Purdue, $34 million by Janssen, and $10 million by Endo.

45. Defendants sent their sales representatives to prescribers based on their specialties and prescribing habits obtained from sales data through IMS Health. Defendants used this data to monitor, and thereby target, specific physicians through the initial and renewal prescribing rates. To ensure that their sales representatives were properly incentivized, Defendants motivated them through bonuses. In 2001, Purdue paid $20 million in "sales incentive bonuses" to its sales representatives.[53]

46. Defendants also utilized "influence mapping" to use decile rankings or similar breakdowns to identify high-volume prescribers. The underlying strategy was that detailers would have the biggest sales impact on high-volume prescribers. For example, Endo identified prescribers representing 30% of its nationwide sales volume and planned sales visits three times per month to these physicians. These detailers visited physicians across the nation, including physicians in Newton County. Defendants also had access to data from IMS Health, which provides Defendants specific details about which medications physicians prescribe and how frequently they do so. This data was collected from more than 50% of the pharmacies in the United States, which would inform Defendants which doctors to target to convince them to prescribe more

[53] Zee, Ex. B, at 2.

opioids or to start prescribing opioids instead of the medications they had been prescribing.

47. Another manner in which Defendants expanded their sales was to target prescribers in individual zip codes and local boundaries. Defendants would send a detailer based on ease of in-person access and the likelihood of convincing the physician to prescribe a higher number of opioids and at higher doses.

48. As part and parcel of their detailing of opioids to physicians, Purdue trained its sales representatives to inform physicians that the risk of addiction was "less than one percent" even though studies demonstrated that there was a high incidence of drug abuse associated with prescription opioid use for chronic pain.[54]

49. As Defendants' marketing efforts grew, they targeted nurse practitioners and physician assistants who, a 2012 Endo business plan noted, were "share acquisition" opportunities because they were more responsive than physicians to details and wrote most of their prescriptions without a physician consult.

50. Studies demonstrate that visits from sales representatives influence the prescribing practices of residents and physicians by curtailing the prescription of generic drugs and rapidly expanding the prescription of new drugs, such as opioids for chronic pain.[55]

51. Defendants also paid doctors to serve on speakers' bureaus, to attend programs, and for meals.[56] In 2017, Dr. Hadland identified some of these payments from pharmaceutical companies to physicians prescribing opioids.[57] It was the first time "industry payments to physicians related to opioid marketing" could be collated because of the "Open Payments program

---

[54] Zee, Ex. B, at 3.
[55] *Id.* at 6.
[56] *See* Scott E. Hadland, M.D., M.P.H, M.S., *Industry Payments to Physicians for Opioid Products, 2013-2015*, 107 Am. J of Pub. Health 9, Sept. 2017, attached hereto as Exhibit C.
[57] *See* Scott E. Hadland, M.D., M.P.H, M.S., *Industry Payments to Physicians for Opioid Products, 2013-2015*, 107 Am. J of Pub. Health 9, Sept. 2017, attached hereto as Exhibit C at 1493.

database" authorized under the "Physician Payments Sunshine Act."[58] Dr. Hadland explained that it was the first large-scale examination of these payments.[59]

52. One statistic Dr. Hadland gleaned from the data is that nearly 1 in 5 family physicians in 2013, out of 108,971 active family physicians, received an opioid-related payment.[60] After culling through the Open Payments program database, Dr. Hadland concluded that "[f]inancial transfers" from pharmaceutical companies to physicians prescribing opioids "were substantial and widespread and may be increasing in number and value."[61]

53. Some of the financial transfers most likely involved speaker programs, which provided: (1) an incentive for doctors to prescribe a particular opioid (so they might be selected to promote the drug); (2) recognition and compensation for the doctors selected as speakers; and (3) an opportunity to promote the drug through the speaker to his or her peers. These speakers gave the false impression that they were providing unbiased and medically accurate presentations when they were, in fact, presenting a script prepared by Defendants. On information and belief, these presentations conveyed misleading information, omitted material information, and failed to correct Defendants' prior misrepresentations about the risks and benefits of opioids.

54. Defendants employed the same marketing plans, strategies, and messages in and around Newton County, Texas as they did nationwide. Across the pharmaceutical industry, "core message" development is funded and overseen on a national basis by corporate headquarters. This comprehensive approach ensures that Defendants' messages are accurately and consistently delivered across marketing channels and in each sales territory. Defendants consider this high level of coordination and uniformity crucial to successfully marketing their drugs.

---

[58] Hadland, Ex. C.
[59] *Id.* at 1495.
[60] Hadland, Ex. C, at 1494.
[61] *Id.* at 1495.

2. Defendants Used a Diverse Group of Seemingly Independent Third Parties to Spread False and Deceptive Statements about the Risks and Benefits of Opioids.

55. Defendants also deceptively marketed opioids in and around Newton County through unbranded advertising. This advertising was ostensibly created and disseminated by independent third parties. But by funding, directing, reviewing, editing, and distributing this unbranded advertising, Defendants controlled the deceptive messages disseminated by these third parties and acted in concert with them to falsely and misleadingly promote opioids for treating chronic pain. Unbranded advertising also avoided regulatory scrutiny because Defendants did not have to submit it to the FDA, and therefore it was not reviewed by the FDA. But it is illegal for a drug company to distribute materials that exclude contrary evidence or information about the drug's safety or efficacy that "clearly cannot be supported by the results of the study."[62] Moreover, a drug company cannot compare or suggest that its "drug is safer or more effective than another drug...when it has not been demonstrated to be safer or more effective in such particular by substantial evidence of substantial clinical experience."[63] It is therefore Defendants' responsibility to ensure that not only is its label accurate and complete, but that any and all materials they distribute is accurate and complete.[64]

56. Defendants' deceptive unbranded marketing often contradicted their branded materials. For example, Endo's unbranded advertising contradicted its concurrent, branded advertising for Opana ER:

---

[62] 21 C.F.R. § 99.101(a)(4).
[63] 21 C.F.R. § 202.1 (e)(6)(ii).
[64] *See* 21 C.F.R. § 201.56 (providing general requirements for prescription drug labeling); 21 C.F.R. § 314.70(c)(6)(iii)(A-C) (providing for changes to labels that strengthen precautions, warnings, or adverse reactions, as well as statements about drug abuse, dependence, or overdosage); *see also Wyeth v. Levine*, 555 U.S. 555 (2009) (holding that a drug company bears responsibility for the content of its drug label at all times).

Pain: Opioid Therapy (Unbranded)	Opana ER Advertisement (Branded)
"People who take opioids **as prescribed usually do not become addicted.**"	"All patients treated with opioids require careful monitoring for signs of abuse and addiction, since **use of opioid analgesic products carries the risk of addiction even under appropriate medical use.**"

57. Drug companies that make, market, and distribute opioids are generally subject to rules requiring truthful marketing of prescription drugs. A drug company's branded marketing, which identifies and promotes a specific drug, must: (a) be consistent with its label and supported by substantial scientific evidence; (b) not include false or misleading statements or material omissions; and (c) fairly balance the drug's benefits and risks.[65]

58. This framework ensures that drug companies, which are best suited to understand the properties and effect of their drugs, bear the responsibility of providing accurate information so that prescribers and users can assess the risks and benefits of the drugs.

59. Defendants did not follow this framework in assisting, creating, and/or distributing third-party publications that included warnings and instructions either mandated by the FDA-required drug labels or that described the risks and benefits known to Defendants. The publications either failed to disclose the risk of addiction and misuse or affirmatively denied the risk of addiction. The publications also "appeared" to be independent third-party materials that had the effect of carrying more weight and credibility to convince physicians that opioids were safe for chronic pain.

a. Defendants Utilized Treatment Guidelines to Promote their Deception.

60. Defendants used treatment guidelines to normalize the use of opioids for chronic

[65] 21 U.S.C. § 352(a); 21 C.F.R. §§ 1.21(a); 202.1(e)(3); 202.1(e)(6).

pain. Doctors, especially general practitioners and family doctors, rely upon treatment guidelines when faced with patients complaining of chronic pain. Scientific literature references treatment guidelines in making its conclusions and third-party payers use treatment guidelines to determine coverage. Even Endo's internal documents indicate that sales representatives discussed treatment guidelines with doctors during individual sales visits.

1. The FSMB Wrote or Sponsored Misleading and Deceptive Guidelines.

61. Headquartered in Euless, Texas, the Federation of State Medical Boards ("FSMB") is a trade organization representing the various state medical boards in the United States. The state boards that comprise the FSMB membership have the power to license doctors, investigate complaints, and discipline doctors. The FSMB finances opioid and pain-specific programs through grants from Defendants.

62. In 1998, the FSMB developed *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* ("FSMB Guidelines"), which was produced in collaboration with pharmaceutical companies. The FSMB guidelines instructed that opioids were "essential" for the treatment of chronic pain, even as a first prescription option.

63. A book adapted from the 2007 FSMB guidelines, *Responsible Opioid Prescribing: A Physician's Guide* ("*Opioid Prescribing*"), released March 1, 2009 makes these same claims. *Opioid Prescribing* was supported by a consortium of pharmaceutical companies and Front Groups with an interest in ensuring that "effective" pain management included the use of opioids.

64. The author of *Opioid Prescribing*, Scott Fishman, M.D., chaired the board and was past president of the American Pain Foundation and served as president of the American Academy of Pain Medicine and served on the board of directors. *Opioid Prescribing* was sponsored by the Alliance of State Pain Initiatives, Federation of State Medical Boards, and the University of

Wisconsin School of Medicine and Public Health.[66]

65. Dr. Fishman was a paid consultant to Cephalon and Eli Lilly. Dr. Fishman was also a paid consultant, on the Speakers' Bureau, and part of the research support for Endo, Merck, Janssen, Pfizer and Purdue.[67]

66. *Opioid Prescribing* was designed for continued medical education ("CME") in which a physician had to read the book, complete questions, and fulfill administrative steps to receive 7.5 hours of credit. The first page of *Opioid Prescribing* specifically states that opioids are the "drugs of choice" and "essential in the treatment of persons with chronic non-cancer pain" and that the CME will inform physicians about the laws and regulations governing the prescribing of opioids for pain control.[68] It also specifically teaches physicians how to protect their practices from unwarranted federal scrutiny.[69]

67. *Opioid Prescribing* marketed "[o]pioid analgesics" as the "drugs of choice for the management of moderate to severe pain . . . [which] may be ***essential*** in the treatment of persons with chronic non-cancer pain."[70] The goal was to "change patient care, medical knowledge, practice-based learning, interpersonal and communication skills, and professionalism . . . ."[71] The argument was that opioids were "underutilized" despite their "effectiveness."[72] The truth, known to Dr. Fishman and Defendants herein, was that using opioids "for other than legitimate medical purposes pose[d] a threat to the individual and society," posed high risks for overdose and addiction, and remained unproven as safe and effective for the long-term treatment of non-cancer

---

[66] Scott M. Fishman, M.D., *Responsible Opioid Prescribing, A Physician's Guide*, FSMB Foundation, Waterford Life Sciences, 2009.
[67] *Id.*
[68] *Id.*
[69] *Id.*
[70] *Id.* at i.
[71] *Id.*
[72] *Id.*

pain.[73]

68. It was even conveyed to doctors that undertreating pain would be officially disciplined whereas doctors prescribing opioids for chronic pain would not be disciplined. *Opioid Prescribing* described a case in which a physician was sued for "elder abuse" and the jury awarded $1.5 million to the plaintiff as an example of a physician that had been "successfully sued for not treating pain aggressively."[74] *Opioid Prescribing* cautioned that "these legal precedents sound a warning that there are risks associated with under-treating."[75] In actuality, it was a threat that doctors would be punished if they *failed* to prescribe opioids to patients who complained about pain. That teaching has held true given that according to the National Safety Council, 67% of doctors prescribe opioids, in part, based on a patient's expectations.[76] Moreover, approximately 74% of doctors incorrectly believe morphine and oxycodone are the most effective ways to treat pain even though research shows that over-the-counter medications such as ibuprofen and acetaminophen are the most effective pain relief for acute pain.[77]

69. Defendants also allayed any concerns doctors may have about patients exhibiting addictive behavior by highlighting the now debunked myth of "pseudoaddiction." Dr. Fishman described pseudoaddiction as a sign that patients were receiving an inadequate dose to obtain pain relief, not as a sign that the patient was exhibiting drug-seeking or addictive behavior.[78]

70. *Prescribing Opioids* taught physicians that the following signs were evidence of "pseudoaddiction" and *not* drug seeking behavior or signs of addiction so long as prescribing additional opioids resolves the pain:

---

[73] Fishman *supra*, at 6, 9.
[74] *Id.* at 28.
[75] Fishman, *supra*.
[76] National Safety Council, *supra*.
[77] *Id.*
[78] Fishman, *supra*, at 62.

- Requesting analgesics by name;
- Demanding or manipulative behavior,
- Clock watching;
- Taking opioid drugs for an extended period;
- Obtaining opioid drugs from more than one physician; and
- Hoarding opioids.[79]

71. Indeed, the types of behaviors that Dr. Fishman posed as "MORE indicative of addiction" included:

- Stealing money to obtain drugs;
- Performing sex for drugs;
- Stealing drugs from others;
- Prostituting others for money to obtain drugs;
- Prescription forgery; and
- Selling prescription drugs.[80]

72. Certainly by the time a patient is performing sex for drugs, the patient has long been addicted and exhibited addictive behavior that was ignored by physicians at the explicit direction of Defendants. This conclusion is supported by the American Psychiatric Association.

73. In the DSM-IV, addiction is "manifested" by three (or more) of the following in a 12-month period, including:

a) Tolerance described as:

> A need for markedly increased amounts of the substance to achieve intoxication or the desired effect
>
> *or*

[79] Fishman *supra.*
[80] *Id.* at 63.

Markedly diminished effect with continued use of the same amount of the substance;

b) Withdrawal manifested by:

The characteristic withdrawal syndrome for the substance

or

The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms;

c) The substance is taken in larger amounts or over a longer period than intended; and

d) Spending a great deal of time to obtain the substance, such as visiting multiple doctors or driving long distances.[81]

74. According to Defendants, as seen in *Prescribing Opioids* and other publications, signs of addiction as defined by the American Psychiatric Association are <u>not</u> signs of addiction, but of pseudoaddiction that justifies taking *more* opioids for a longer period of time.

75. The reason not to discontinue the use of opioids – indeed, the foundation upon which Defendants built its opioid empire – was "the undertreatment of pain."[82] *Opioid Prescribing* claimed the undertreatment of pain has "been recognized as a public health crisis for decades. The cost of human suffering is immeasurable. Turning away patients in pain simply is not an option."[83] However, according to Dr. Donald Treater, medical advisor at The National Safety Council: "Opioids do not kill pain; they kill people."[84]

---

[81] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Ed., Washington, D.C., American Psychiatric Assoc., 2000.
[82] Fishman, *supra*, at 105.
[83] Fishman, *supra*; *see also id.* at 80 (stating that efforts have been made to reduce the undertreatment or non-treatment of pain in children, the elderly, and in other vulnerable patient populations).
[84] National Safety Council, *supra*.

76. *Prescribing Opioids* acknowledged that by 2005, more than 10 million Americans were abusing prescription drugs, which is more than the combined number of people abusing cocaine, heroin, hallucinogens, and inhalants combined.[85] It also acknowledged that prescription opioids are associated with more overdose deaths than cocaine and heroin combined.[86] Yet the book then cautioned that the "undertreatment" of non-cancer pain was a public health crisis of equal importance that justified more opioid prescribing.

77. Under the guise of addressing "legitimate cause of undertreated pain" that "patients and advocates have been pushing to address,"[87] Defendants tailored opioid marketing campaigns to affect children and the elderly. The Defendants made significant efforts to promote more opioid prescribing for "untreated or undertreated pain in children, older patients, and in all other vulnerable patient populations."[88]

78. Defendants also taught physicians that "[p]ain is what the patient says it is" and that a physician "cannot measure or even confirm the pain that a patient is experiencing."[89] As such, "pain remains an untestable hypothesis."[90] Furthermore, "[p]atients should not be denied opioid medications except in light of clear evidence that such medications are harmful to the patient."[91] All in all, opioids would cure the "pain epidemic" facing Americans. And yet, chronic pain continues to be a problem facing Americans, as well as an opioid epidemic of addiction and death.

79. A total of 200,000 copies of *Opioid Prescribing*, which Dr. Fishman wrote for the FSMB, has been delivered to U.S. prescribers through 20 state medical boards, including Texas.[92]

---

[85] *Responsible Opioid Prescribing, supra,* at 6.
[86] *Id.*; *Prescribing Opioids* even recognized that "[b]ehind these figures lie millions of individual stories of personal tragedy: untimely death, fractures families, shattered dreams and wasted lives." *Id.* at 7.
[87] *Id.* at 8.
[88] Fishman, *supra*, at 8.
[89] *See id.* at 14.
[90] *Id.* at 13.
[91] *Id.* at 9.
[92] Scott M. Fishman, M.D., *Listening to Pain,* Oxford Univ. Press, 2012, at 135.

The FSMB earned approximately $250,000 from the sale. The FSMB website describes the book as the "leading continuing medication education (CME) activity for prescribers of opioid medications."

80. The guidelines for *Opioid Prescribing* were posted online for use and reliance by physicians throughout America, including but not limited to, those servicing patients in Newton County. State medical boards even encouraged physicians to buy the book and participate in the CME. The North Carolina Medical Board stated on its website that *Prescribing Opioids* "has been ***widely used and supported*** in the medical and regulatory communities as the leading continuing medical education (CME) activity for prescribers of opioid medications."[93] The website then informs physicians that a CME accompanies the book and directs them to the book and how to claim the CME. The FSMB also hosted free CMEs in Texas, including Houston, Dallas, and Austin, related to extended-release and long-acting opioids.[94] The CME taught physicians the "safe and responsible prescribing of opioid medications and [was] aimed at improving prescriber training and counseling for patients while providing more thorough information on extended-release or long-acting (ER/LA) opioid products on the market."[95]

81. The impact of *Opioid Prescribing* was even studied through a survey sent to 12,666 licensed Georgia physicians six weeks after receiving the book.[96] The lead author was a member of FSMB.[97] A total of 508 physicians completed the online survey and of those, 82.1% rated the

---

[93] North Carolina Medical Board, *FSMB Foundation Publishes Second Edition of Prescribing Book*, Forum Newsletter, July 31, 2012; *see also* University of Wisconsin School of Medicine and Public Health, Federation of State Medical Boards, *Responsible Opioid Prescribing – Book Helps Physicians Reduce Risk of Opioid Diversion and Abuse*, April 1, 2009 (describing the book and CME activity).
[94] Texas Medical Board, *Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy*, www.tmb.state.tx.us.
[95] *Id.*
[96] A. Young, *Physician Survey Examining the Impact of an Educational Tool for Responsible Opioid Prescribing*, J. Opioid Management, Mar-Apr. 2012.
[97] *Id.*

book either "very good" or "good" for improving care for their patients in pain.[98] Almost one-third (32.2%) claimed that they intended to make changes to their practice after reading the book.[99] Of note, 42.8% of solo practitioners and 41.6% of primary care providers were more likely to make changes to their practice than doctors in other areas.[100] Of the respondents, 57.7% said that the book was better than others with regard to prescribing opioids and on pain management.[101]

82. *Opioid Prescribing* was therefore an effective tool that impacted specific doctors and their prescribing practices, as concluded by the study. Specifically, the study provided "insight into which physician population would be the most receptive to the type of information presented in Dr. Fishman's book" and that population was to "first target[] solo and primary care physicians."[102] Defendants found out that their educational efforts "significantly altered prescription practices."[103]

2. The Joint Commission also Spread Deceptive Information.

83. The Joint Commission on Accreditation of Healthcare Organizations ("JCAHO") is a United States-based non-profit, tax-exempt organization that "accredits and certifies nearly 21,000 health care organizations and programs in the United States."[104] A majority of state governments recognize accreditation from the Joint Commission as a condition of licensure and for receiving Medicaid and Medicare reimbursements.[105] CHRISTUS Jasper Memorial Hospital in Jasper, Texas, which is the main hospital that feeds into Newton County, is accredited by and

---

[98] *Id.*
[99] *Id.*
[100] *Id.*
[101] *Id.*
[102] *Id.*
[103] *Id.*
[104] www.jointcommission.org.
[105] Anthony Anonimo, *Poppy Seed. Revealing the Roots of the Opioid Epidemic*, Trinity Mother Frances Health System, 2017, at 65.

subscribes to the JCAHO.[106]

84. According to the JCAHO, it "continuously improve[s] health care for the public" and inspires health care organizations "to excel in providing safe and effective care of the highest quality and value."[107] The JCAHO is not independent, but has been influenced by Defendants and those Defendants used the JCAHO as a marketing shill to spread the misleading message that opioids are non-addictive and safe as a first-line analgesic to treat any complaint of pain.

85. In 2000, the JCAHO published *Pain Assessment and Management: An Organizational Approach* ("*Pain Assessment*"), which was paid for by Purdue and reviewed by June L. Dahl, Ph.D., who has worked for Abbott, Endo, and Purdue.[108]

86. The JCAHO mission statement on the inside cover page of the book explains that it aspires "to continuously improve the safety and quality of care provided to the public through the provision of health care accreditation and related services that support the performance improvement in health care organizations."[109] One of its big achievements, however, is its endorsements of new pain management standards that underscored Defendants' fraudulent message.

87. JCAHO, with the help of the American Pain Society ("APS"), a Front Group, loosened pain management standards thereby allowing doctors to prescribe opioids for any complaint of pain. To that end, "[t]he Joint Commission recognize[d] pain as a major, yet largely avoidable, problem . . . .[and] has expanded the scope of its pain management standards, which have been endorsed by the American Pain Society (APS), ***to cover all pain scenarios in accredited***

[106] www.jointcommission.org.
[107] *Id.*
[108] Joint Commission on Accreditation of Healthcare Organizations, *Pain Assessment and Management*, 2000.
[109] *Id.*

health care organizations rather than limiting the scope to end-of-life care."[110] (Emphasis added.) On January 1, 2001, Texas incorporated JCAHO pain management standards for hospital and healthcare group accreditation.[111] The Texas Medical Association advertises that *Pain Assessment* "provides practical help in integrating pain assessment and management into organizational systems . . . ."[112]

88. *Pain Assessment* established the cornerstone of Defendants' message that "all pain scenarios" should be included in pain management practices.[113] It explained that "[p]ain is the most common reason individuals seek medical attention. According to the American Pain Society (APS), 50 million Americans are partially or totally disabled by pain."[114] "The conclusion? Pain is undertreated – despite the availability of effective pharmacologic and nonpharmacologic therapies. Why?"[115]

89. The answer is on the first page of *Pain Assessment*. There is a chronic pain epidemic. Chronic pain is undertreated. Chronic pain can be managed and even cured with opioids, which are safe and effective, according to *Pain Assessment*. And the JCAHO encouraged organizations to establish standards for recording and responding to patient pain reports and monitoring staff performance and compliance with those standards, so that a physician who did not agree with the JCAHO standards faced the specter of poor performance evaluations.[116]

90. According to *Pain Assessment*, the reasons healthcare professionals had not used opioids previously included: (1) inadequate knowledge of opioids pharmacology and pain therapy,

---

[110] *Pain Assessment, supra.*
[111] Texas Medical Association, *JCAHO Pain Management Services, available at* https://www.texmed.org/Template.aspx?id=2389&terms=The%20war%20on%20pain.
[112] *Pain Assessment, supra.*
[113] *Pain Assessment, supra,* at p. 1.
[114] *Id.*
[115] *Id.*
[116] *Pain Assessment, supra,* at 41-42.

(2) poor pain assessment practices, (3) unfounded concerns about regulatory oversight, and (4) fear of opioids' side effects such as tolerance and addiction.[117]

91. *Pain Assessment* asserted that few practitioners received adequate training in pain management in medical school or during their residency resulting in the failure to prescribe opioids or nonsteroidal anti-inflammatory drugs (NSAIDS) on a regular basis leaving patients without pain relief.[118] "[Many] health care professionals lack the knowledge and skills to manage pain effectively, and they fear the effects of treatment."[119] Too few health care systems make pain management a priority.[120] Some clinicians had "inaccurate and exaggerated concerns about addiction, tolerance, respiratory depression, and other opioid side effects, which lead them to be extremely cautious about the use of drugs."[121] Instead of expanding upon and explaining the risks of opioids, *Pain Assessment* states: "***This attitude prevails despite the fact there is no evidence that addiction is a signification issue when persons are given opioids for pain control.***"[122] (Emphasis added). That claim of insignificant addiction risk was false when made and remains false today. Yet it worked as intended to mislead treating doctors, medical staff, and patients into believing opioids could and should be utilized more often. Indeed, 74% of doctors "incorrectly believe morphine and oxycodone" are the "most effective ways to treat pain" even though research shows that over-the-counter pain relievers are the most effective for acute pain.[123] Even worse, 20% of doctors prescribing opioids prescribed at least a month's worth, even though the evidence shows that "30-day use causes brain changes."[124]

---

[117] *Pain Assessment, supra.*
[118] *Id.*
[119] *Id.* at 3.
[120] *Id.* at 1.
[121] *Pain Assessment, supra,* at 4.
[122] *Id.*
[123] National Safety Council, *supra.*
[124] *Pain Assessment, supra.*

92. Patients also contributed to the pain epidemic by their reluctance to report their pain and to take medications,[125] according to *Pain Assessment.* Doctors were instructed to engage patients in conversations about their pain before prescribing opioids by: (1) asking for pain relief when the pain begins; (2) helping the doctor or nurse assess the pain; and (3) telling the doctor or nurse if the pain is not relieved.[126] Doctors were taught that "[t]he single most reliable indicator of the existence and intensity of pain is the individual's self-report."[127] Indeed, the individual's self-report was to be the ***primary*** source of information for the doctor and deemed more reliable than the observations of others.[128]

93. The bombardment of information, instruction, books, pamphlets, seminars, ads, and marketing regarding this "pain epidemic" was so successful that pain has been included as the "fifth vital sign" to be recorded along with the individual's temperature, pulse, respiration, and blood pressure.[129] This strategy was first pitched by the APS to ensure that pain management gained acceptance in the medical community, which it did.[130]

94. Beginning in 1999, the Veteran's Health Administration began routinely assessing pain as the fifth vital sign in every individual.[131] And according to *Pain Assessment*, the research showed that "when pain assessment information is included in clinical charts, those individuals' analgesics [meaning opioids] are more likely to be increased."[132] In other words, including pain as a fifth element results in not only the prescribing of more opioids, it results in the prescribing of higher doses of opioids.

---

[125] *Pain Assessment, supra*, at 4.
[126] *Id.* at 8.
[127] *Id.* at 13.
[128] *Id.*
[129] *Pain Assessment, supra*, at 20.
[130] *See id.* 20-21.
[131] *Id.* at 21.
[132] *Pain Assessment, supra.*

95. *Pain Assessment* also framed the role of key opinion leaders ("KOL") as trustworthy people "to evaluate new clinical information, assess new practices, and then determine their value within the context of the local setting."[133] Doctors were expected to accept KOLs opinions even though KOLs are ***not*** "necessarily innovators or authority figures."[134] KOLs convinced practitioners that their current chronic pain treatment was "outdated, inappropriate, unsupported by research evidence, or no longer accepted by colleagues."[135]

96. Expert leaders, on the other hand, influenced and implemented protocols with individuals or small groups.[136] These "academic strategies" included "conducting interviews to determine baseline knowledge, stimulating active participation during educational sessions, using concise graphic educational materials, and highlighting or replicating essential messages."[137] Academic detailing was modeled after pharmaceutical detailing practices in which representatives visited physicians to talk about specific medicines, just as Defendants' representatives met with physicians to about opioids.[138] Simply put, *Pain Assessment* was a part of a marketing campaign to plow ground for Defendants to sell more opioids, and the book set forth sophisticated, multi-layered marketing strategies that were most effective in executing the campaign.

97. If a doctor was not available to prescribe opioids, a nurse would suffice. A nurse specializing in oncology, surgery, critical care, or a nurse anesthetist, as well as a clinical pharmacist, can "serv[e] as role models, provid[e] pain management education and consultation, and act[s] as agents of change."[139] These educational efforts "significantly altered prescription

---

[133] *Pain Assessment*, *supra*, at 24.
[134] *Id.*
[135] *See id.* at 25.
[136] *Id.*
[137] *Pain Assessment*, *supra*, at 25.
[138] *See id.*
[139] *Pain Assessment*, *supra*.

practices."[140]

98. To succeed in prescribing opioids for chronic pain, Defendants had to create a market for chronic pain. To do so, Defendants literally encouraged patients not to tolerate pain and to fear pain *more* than opioid addiction.[141] Physicians and their staff were encouraged to educate their patients about "effective pain management," which included the use of opioids.[142] *Pain Assessment* explained research that showed Americans would rather bear pain because they were afraid of "addiction, dependence on drugs, and tolerance to medications," which affected not only the patient's willingness to report pain, but to use adequate amount of opioids to control the pain.[143] A patient's reluctance to take opioids out of fear they would not function normally meant that the problem was "underreported" and the pain went "untreated."[144]

99. Consequently, the answer was to inform and educate the patient that unrelieved pain is harmful and that he or she should communicate pain.[145] *Pain Assessment* instructed the use of pain assessment instruments, including pain intensity scales, to describe the nature of the pain and stressed that the "most reliable indicator of pain" was the individual's self-report.[146] Once the patient reported the pain, the physicians and staff were taught to tell the patient about opioids, explain that opioids were safe and effective, describe the name, dosage, and duration of the opioid therapy, and explain the risk of pain versus the importance of pain management.[147]

100. To ensure that patients self-reported pain prior to hospital visits, *Pain Assessment* encouraged health care systems to provide individuals and families with pain management

---

[140] *Pain Assessment, supra.*
[141] *Id.* at 33.
[142] *Id.*
[143] *Id.*
[144] *Pain Assessment, supra*, at 33.
[145] *Id.* at 35.
[146] *Id.*
[147] *Id.*

information ***prior*** to being admitted.[148] And health care systems were told to leave individuals and family members with audio and videotapes to watch and listen to about the "importance" of "pain relief" so that they truly understood the message – that is, if you have "pain," tell us and we will provide opioids.

101. The JCAHO was not independent and did not improve the safety or quality of healthcare. Instead it was hijacked by Defendants to standardize pain management criteria that required the use of opioids for chronic pain. The JCAHO was merely a pawn in the Defendants' larger game.

102. Like other books and pamphlets used by Defendants to spread their "message," *Pain Assessment* was distributed throughout the nation and in Texas. As of today, anyone can buy a used copy of *Pain Assessment* on Amazon.com for $26.48 plus $5.99 in shipping costs from a seller in Texas.

b. Key Opinion Leaders (KOLs) were another Means of Disseminating False Information.

103. Defendants also sponsored KOLs, a small circle of doctors who, upon information and belief, were selected, funded, and elevated by Defendants because they publicly supported dispensing opioids more widely and indiscriminately.

104. Defendants paid KOLs to serve as consultants or to appear on their advisory boards and to give talks or present CMEs, and Defendants' support helped these KOLs become respected industry experts. As they rose to prominence, these KOLs promoted the benefits of opioids to treat chronic non-cancer pain, repaying Defendants by advancing their marketing goals.

105. KOLs wrote articles and books, gave speeches, and taught CMEs to promote the utilization of opioids to treat moderate non-cancer pain. Defendants created opportunities for

[148] *Pain Assessment, supra,* at 36.

KOLs to participate in "studies" and write papers for the purpose of advancing Defendants' marketing theme: opioids should be dispensed regularly and perpetually to treat a broad array of pain complaints.

106. Defendants' KOLs also served on committees that developed treatment guidelines that strongly encourage using opioids to treat chronic pain, and on the boards of pro-opioid advocacy groups and professional societies that develop, select, and present CMEs. Defendants were able to direct and exert control over each of these activities through their KOLs.

107. Pro-opioid doctors are one of the most important avenues that Defendants use to spread their false and deceptive statements about the risks and benefits of long-term opioid use. Defendants know that doctors rely heavily and less critically on their peers for guidance, and KOLs provide the false appearance of unbiased and reliable support for using opioids for chronic pain.

108. Different Defendants utilized many of the same KOLs. Two of the most prominent are described below.

1. Russell Portenoy

109. Dr. Russell Portenoy, former Chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York, is one example of a KOL who Defendants identified and promoted to further their marketing campaign. Dr. Portenoy received research support, consulting fees, and honoraria from Endo, Janssen, and Purdue (among others), and was a paid consultant to Purdue.

110. Dr. Portenoy was instrumental in opening the door for the regular use of opioids to treat chronic pain. He served on the American Pain Society ("APS")/American Academy of Pain Medicine ("AAPM") Guidelines Committees, which endorsed the use of opioids to treat chronic pain, first in 1997 and again in 2009. He was also a member of the board of the American Pain

Foundation ("APF"), an advocacy organization almost entirely funded by Defendants.

111. Dr. Portenoy also made frequent media appearances promoting opioids. He appeared on *Good Morning America* in 2010 to discuss using opioids long-term to treat chronic pain. On this widely-watched program, broadcast in Texas and across the country, Dr. Portenoy claimed: "Addiction, when treating pain, is distinctly uncommon. If a person does not have a history, a personal history, of substance abuse, and does not have a history in the family of substance abuse, and does not have a very major psychiatric disorder, most doctors can feel very assured that that person is not going to become addicted."[149]

112. Perhaps realizing that "[m]ore than 16,000 people die from opioid overdoses every year," Dr. Portenoy is now having "second thoughts" about the "wider prescription" of drugs like Vicodin, OxyContin, and Percocet.[150] Dr. Portenoy later admitted in a 2010 videotaped interview that he "gave innumerable lectures in the late 1980s and '90s about addiction that weren't true."[151] According to Dr. Portenoy, because the primary goal was to "destigmatize" opioids, he and other doctors promoting them overstated their benefits and glossed over their risks.

113. Dr. Portenoy put doctors' fear that opioids were dangerous and addictive, and meant only for cancer patients, to rest by arguing that they could be taken safely for months, even years, by patients with chronic pain.[152] Dr. Portenoy, as well as other doctors making the speaker rounds, asserted that "[l]ess than 1% of opioid users became addicted, the drugs were easy to discontinue and overdoses were extremely rare in pain patients."[153]

---

[149] Good Morning America television broadcast, ABC News, Aug. 30, 2010.
[150] Thomas Catan & Evan Perez, *A Pain-Drug Champion Has Second Thoughts*, WALL ST. J., Dec. 17, 2012, attached hereto as Exhibit D.
[151] *Id.*
[152] Catan, *supra*.
[153] Catan, *supra*.

114. Dr. Portenoy also conceded that "[d]ata about the effectiveness of opioids does not exist."[154] Dr. Portenoy candidly stated: "Did I teach about pain management, specifically about opioid therapy, in a way that reflects misinformation? Well...I guess I did."[155]

115. Before his moment of clarity, Dr. Portenoy co-authored a guide to publicize the benefits of opioids for chronic pain, which was paid for by an unrestricted education grant from Endo, titled *A Clinical Guide to Opioid Analgesia* ("*Opioid Analgesia*").[156] *Opioid Analgesia* reiterated that opioids are "absolutely necessary" for pain relief.[157]

116. Although *Opioid Analgesia* claimed "to help clinicians make practical sense of the varied and often conflicting pharmacologic, clinical and regulatory issues to promote the most healthful outcomes possible for patients in pain,"[158] the reality was that it expressed regret that federal and state governments had passed controlled substances acts to stem addiction, which had curtailed the prescription of opioids.[159] This regulation, explained *Opioid Analgesia*, "contributed to the underuse of opioid medications."[160]

117. As with all other books, guidelines, and CMEs promoted by Front Groups and KOLs, *Opioid Analgesia* establishes the absolute need for opioids in light of the chronic pain epidemic. "Because pain is inherently subjective, patient self-report is the 'gold standard' for assessment."[161] If there's no discernible reason for the pain, then it should be characterized as "idiopathic."[162] Regardless of how the pain is characterized, the solution, per *Opioid Analgesia,* is opioids.

---

[154] Catan, *supra.*
[155] *Id.*
[156] Perry G. Fine, M.D. and Russell K. Portenoy, M.D., *A Clinical Guide to Opioid Analgesia*, McGraw-Hill, 2004.
[157] *Id.* at 2.
[158] *Id.* at 3.
[159] *Id.*
[160] *Id.* at 6.
[161] Fine, *supra,* at 34.
[162] Fine, *supra,* at 35.

118. "While opioid analgesics are controlled substances, they are also essential medication and are absolutely necessary for relief of pain."[163] "Opioid analgesics should be accessible to all patients who need them for relief of pain."[164] Brushing away any concerns about addiction, *Opioid Analgesia* posits that "[a] patient who has reached middle age without developing compulsive use behaviors to potentially abusable drugs, including alcohol and nicotine, appears to be at a very low risk" of addiction, especially if "there is no family history of addiction."[165]

119. Underplaying the risks of addiction, *Opioid Analgesia* falsely claimed that "[o]verall, the literature provides evidence that the outcomes of the drug abuse and addiction are rare among patients who receive opioids for a short period (i.e., for acute pain) and among those with no history of abuse who receive long-term therapy for medical indications."[166] Even while admitting there is "very little information about the risks of misuse, abuse, or addiction among different opioid-treated populations" and even admitting the "[w]hen misused, opioids pose a threat to society,"[167] Defendants' intentionally marketed opioids as effective and safe for treatment of chronic pain and summed up the risk of addiction for short-term therapy as "rare."[168]

120. Of course when addiction is as narrowly defined as it is in the books, CMEs, and guidelines that Defendants publishes, the risk of addiction would be termed as "rare." The behaviors cited in *Opioid Analgesia* as "probably more suggestive" of addiction included:

- Selling prescription drugs;
- Forging prescriptions;

---

[163] *Id.* at Table 1.
[164] *Id.*
[165] *Id.* at 21.
[166] *Id.*
[167] *Id.* at 31, 2.
[168] Fine, *supra*, at 34.

- Stealing or "borrowing" drugs from others;
- Injecting or inhaling (snorting, smoking) oral formulations; and
- Obtaining the prescription drugs from nonmedical sources.[169]

121. Whereas the following behaviors are "probably less suggestive" of addiction:

- Aggressive complaining about the need for more drug;
- Drug hoarding during periods of reduced symptoms;
- Requesting specific drugs; and
- Using the drug, without approval, to treat another symptom.[170]

122. Instead of these behaviors being symptoms of possible addiction, Dr. Portenoy terms these behaviors as a "phenomenon" termed "pseudoaddiction."[171] Pseudoaddiction allows physicians to discount these behaviors because "they are driven by desperation surrounding unrelieved pain" and are "eliminated by measures that relieve the pain, such as an increase in medication."[172] Instead of treating the "less suggestive" symptoms for what they are – signs of addiction.

123. *Opioid Analgesic* was a success for Defendants in that it has been and continues to be used extensively in CMEs, pamphlets, and reading lists for physicians looking for information regarding opioids. For example, *Opioid Analgesia* was cited ***just last year*** in a presentation at the University of North Texas College of Pharmacy on April 28, 2017, entitled *Adverse Drug Events Associated with Opiate-Based Pain Management* (Emphasis added). It has also been listed as a reference for a CME entitled *The Management of Opioid-Induced Constipation* published by the University of North Texas Health Science Center, which was valid for CME from May 2009 to

[169] Fine, *supra*, at 85.
[170] *Id.*
[171] *Id.* at 35.
[172] *Id.*

May 2010. Finally, the book was included in the suggested reading list for a seminar entitled *When Opioids Are Indicated for Chronic Pain* presented on March 26, 2011, in Houston, Texas.

2. Lynn Webster

124. Another KOL, Dr. Lynn Webster, was the co-founder and Chief Medical Director of Lifetree Clinical Research, an otherwise-unknown pain clinic in Salt Lake City, Utah. Dr. Webster was President in 2013 and is a current board member of AAPM, a Front Group that ardently supports using opioids for chronic pain. He is a Senior Editor of *Pain Medicine*, the same journal that published Endo special advertising supplements recommending Opana ER. Dr. Webster authored numerous CMEs sponsored by Endo and Purdue while he was receiving significant funding from Defendants.

125. In 2011, Dr. Webster presented a program via webinar sponsored by Purdue titled *Managing Patient's Opioid Use: Balancing the Need and the Risk*. Dr. Webster recommended using risk screening tools, such as urine testing and patient agreements as a way to prevent "overuse of prescriptions" and "overdose deaths," which was available to and was intended to reach doctors treating Newton County residents.

126. Dr. Webster also was a leading proponent of the concept of "pseudoaddiction," the notion that addictive behaviors should be seen not as warnings, but as indications of undertreated pain. In Dr. Webster's description, the only way to differentiate the two was to *increase* a patient's dose of opioids. As he and his co-author wrote in a book entitled *Avoiding Opioid Abuse While Managing Pain* (2007), a book that is still available online, when faced with signs of aberrant behavior, increasing the dose "in most cases . . . should be the clinician's first response." Endo distributed this book to doctors.

127. Years later, Dr. Webster reversed himself, acknowledging that "[pseudoaddiction] obviously became too much of an excuse to give patients more medication."[173] Dr. Webster also admits that "[i]t's obviously crazy to think that only 1% of the population is at risk for opioid addiction."[174]

c. Front Groups Affirmed Defendants' Falsities.

128. Defendants entered into arrangements with seemingly unbiased and independent patient and professional organizations to promote opioids for treating chronic pain. Under Defendants' direction and control, these "Front Groups" generated treatment guidelines, unbranded materials, and programs that favored using opioids for chronic non-cancer pain. They also assisted Defendants by responding to negative articles, by advocating against regulatory changes that would limit prescribing opioids in accordance with the scientific evidence, and by conducting outreach to vulnerable patient populations targeted by Defendants.

129. These Front Groups depended on Defendants for funding and, in some cases, for survival. Defendants also exercised control over programs and materials created by these groups by collaborating on, editing, and approving their content, and by funding their dissemination. In doing so, Defendants made sure these Front Groups would generate only the messages Defendants wanted to distribute. Even so, the Front Groups held themselves out as independent and as serving the needs of their members – whether patients suffering from pain or doctors treating those patients.

130. Defendants Endo, Janssen, and Purdue utilized many Front Groups, including many of the same ones. Several of the most prominent are described below, but there are many others, including the American Pain Society ("APS"), American Geriatrics Society ("AGS"), the Federation of State Medical Boards ("FSMB"), American Chronic Pain Association ("ACPA"),

[173] John Fauber & Ellen Gabler, *Networking Fuels Painkiller Boom*, MILWAUKEE WISC. J. SENTINEL, Feb. 19, 2012.
[174] Thomas Catan & Evan Perez, *A Pain-Drug Champion Has Second Thoughts*, WALL ST. J., Dec.17, 2012.

American Society of Pain Education ("ASPE"), National Pain Foundation ("NPF") and Pain & Policy Studies Group ("PPSG").

1. American Pain Foundation ("APF")

131. APF was founded in 1997 and professed to be an independent non-profit 501(c)3 organization "serving people with pain through information, advocacy and support."[175] It had a membership of "close to 100,000 and growing" in 2010 and claimed to be the "largest advocacy group for people with pain."[176] The APF lauded its participation in "close to 100 policy activities," which included testifying at legislative hearings to securing state and local proclamations for Pain Awareness Month.[177]

132. APF, however, as the most prominent of Defendants' Front Groups, received more than $10 million in funding from opioid manufacturers from 2007 until it closed its doors in May 2012. Endo alone provided more than half that funding; Purdue was next at $1.7 million. Despite the influx of funds from pharmaceutical companies, APF claimed to be an independent patient advocacy group.

133. In 2009 and 2010, more than 80% of APF's operating budget came from pharmaceutical industry sources. Including industry grants for specific projects, APF received about $2.3 million from industry sources out of total income of about $2.85 million in 2009. In 2010, Endo paid APF more than $1 million and Purdue paid APF between $1 million and 4.9 million.[178] By 2011, APF was entirely dependent on incoming grants from Purdue, Endo, and others to avoid using its line of credit. One of its board members, Russell Portenoy, explained the

[175] American Pain Foundation, *Treatment Options: A Guide for People Living with Pain*, www.painfoundation.org; *see also 2010 Annual Report*, American Pain Foundation.
[176] *2010 Annual Report*, *supra*.
[177] *Id.*
[178] *Id.*

lack of funding diversity was one of the biggest problems at APF.

134. APF issued education guides for patients, reporters, and policymakers that recommended opioids for chronic pain while trivializing their risks, particularly the risk of addiction. Its *Pain Community News*, an "esteemed" quarterly newsletter, had a print circulation of more than 68,000 plus additional online readers.[179] Its monthly electronic newsletter, *Pain Monitor*, was a monthly newsletter that provided links to pain-related news and research.[180] The APF also provided "patient representatives" for Defendants' promotional activities, including Purdue's *Partners Against Pain*[181] and Janssen's *Let's Talk Pain.*[182]

135. In one of its publications, *Treatment Options: A Guide for People Living with Pain*, ("*Treatment Options*"), APF recognized contributions from Cephalon and Purdue.[183] *Treatment Options* was reviewed by Scott Fishman, M.D., Vice Chairman of the APF Board of Directors, and Russell Portenoy, M.D., a Member of the APF Board of Directors and also a KOL.[184] *Treatment Options* set the stage for prescribing opioids by explaining their underuse despite their benefits.[185] It dismissed the risk of addiction with the rhetoric that physical dependence was nothing more than symptoms or signs of withdrawal that occurred when opioids were stopped suddenly or the dose lowered too quickly.[186]

136. *Responsible Opioid Prescribing* and *The War on Pain* both had a tremendous impact on doctors' prescribing habits. In 2000, Scott Fishman, M.D., who served on APF's board,

---

[179] *2010 Annual Report, supra*, at 2.
[180] *Id.* at 2.
[181] In its "Partner against Pain" website, Purdue claimed that the risk of addiction from the use of OxyContin in treating "chronic non-cancer pain" was "extremely small"; *see also* Zee, Ex. B, at 3.
[182] *Let's Talk Pain* was a "coalition effort that focus[ed] on supporting positive patient-provided communications" regarding pain.
[183] *Treatment Options, supra*, at ii.
[184] *Id.* at iv.
[185] *Id.* at 11.
[186] *Id.* at 14 (referring to symptoms such as sweating, rapid heart rate, nausea, diarrhea, goosebumps, and anxiety).

co-authored *The War on Pain* ("*Pain War*") as general authoritative information about pain medicine."[187]

137. *Pain War* seeks new specialties in which opioids can be prescribed for chronic pain. Rheumatologists treating arthritis have been overlooked because they were more prone to prescribe NSAIDS instead of opioids, such as morphine.[188] But such "outdated ideas about addiction and concerns about social stigmas" need to evolve because opioids offer "substantial relief" with "less severe long-term side effects than chronic anti-inflammatories."[189]

138. *Pain War* advocates for physical dependence to opioids, and equates withdrawal symptoms from opioid drugs to that of cessation of coffee drinking. A "pain patient who is dependent on opioids finds life restored," the book advises, and then explains that removing a patient from opioids causes physical, not psychological, consequences, like quitting *coffee*.[190] Addiction to opioids is treated as a "phobia" or "notion" that "using opioids" are "always addictive."[191]

139. *Pain War* censures the failure to prescribe opioids and even suggests that such failure is a criticism of the patient. For example:

> Doses tend to be too low, the right narcotic preparation tends to be avoided, and the prescribing period is often too short. Medicine's reluctance to use appropriate doses of opioid drugs gives patients the wrong message – their pain isn't that important, they are not trustworthy, they may be addicts, they are bad people if they take drugs even if they are prescribed.[192]

140. *Pain War* was distributed across the nation, and sold in Texas, as evidence by a seller from Texas offering the used book for $9.56 plus $5.99 in shipping costs on Amazon.com.

---

[187] Scott Fishman, M.D., with Lisa Berger, *The War on Pain*, First Quill, 1st ed., 2000.
[188] *Id.* at 154.
[189] Fishman, *War on Pain*, *supra*, at *155.*
[190] *Id.* at 187.
[191] *Id.* at 185.
[192] *Id.*

141. As late as 2008, the APF was still relaying the same message. In *A Reporter's Guide: Covering Pain and Its Management* ("*Reporter's Guide*"), the APF extolled that "[t]he person with pain is the authority on the existence and severity of his/her pain. The self-report is [the] most reliable indicator."[193] The *Reporter's Guide* referred to pain as a health crisis and concluded that it affected more Americans than "diabetes, heart disease and cancer combined."[194]

142. Yet APF, Defendants' Front Group also admitted that:

- 71% of people abusing prescription pain relievers received them from a friend or family member without a prescription;
- Approximately 2.2 million Americans abused pain medication for the first time in 2006; and
- Between 1992 and 2002, reported abuse by teenagers increased by 542%.[195]

143. Even though Defendants knew about the risks involved in prescribing opioids or ingesting opioids, they continued to disseminate a story about a "pain epidemic" that could be treated only through the use of opioids. Even a 542% increase in abuse by teenagers in the United States in the span of ten years did not make Defendants change their marketing strategy or otherwise modify their educational or promotional materials concerning the risks associated with the use of opioids.

144. In addition to these publications, APF also engaged in a significant multimedia campaign – through radio, television, and the internet – to educate patients about their "right" to pain treatment, namely opioids. APF's local and national media efforts resulted in 1,600 media stories on pain in 2010, which was an increase of 1,255% from 2009.[196] APF surmised that it

---

[193] American Pain Foundation, *A Reporter's Guide: Covering Pain and Its Management*, Oct. 2008, at 1, attached hereto as Exhibit E.
[194] *Id.* at 29.
[195] *Reporter's Guide*, Ex. E, at 29.
[196] *Reporter's Guide*, *supra*, at 15.

reached more than 600 million people with information and education related to pain.[197] All of the programs and materials were available nationally and were intended to reach patients and consumers in Newton County.

145. APF's website was visited by nearly 275,000 people in 2010 and a National Pain Foundation was expected to be complete in 2011.[198] In May 2012, the U.S. Senate Finance Committee began investigating the financial ties between Front Groups and trade organizations, such as APF and the FSMB, and the opioid manufacturers. This investigation not only caused damage to APF's credibility but caused Defendants to cease its funding.

146. The Senate Finance Committee intended to investigate whether pharmaceutical companies were responsible for the opioid epidemic by "promoting misleading information about the drugs' safety and effectiveness."[199] The Senate Finance Committee was concerned that a "network of national organizations and researchers with financial connections to the makers of narcotic painkillers . . . helped create a body of dubious information 'favoring opioids' that can be found in prescribing guidelines, patient literature, position statements, books and doctor education courses."[200]

147. The Senate Finance Committee was especially concerned that "[a]mong the FSMB's educational initiatives has been the development and distribution of a guidebook intended to help physicians recognize the risk of opioids and follow responsible and safe prescribing standards."[201] (Emphasis in original.) Hence, Dr. Fishman and his book *Opioid Prescribing: A Physician's Guide*, the first edition of which was released in 2007 and later accredited by the University of Wisconsin

---

[197] *Reporter's Guide, supra.*
[198] *2010 Annual Budget, supra,* at 6
[199] *See* Letter to Dr. Humayun J. Chaudhy dated May 8, 2012 from Charles E. Grassley and Max Baucus, at p. 2.
[200] *Id. quoting* Milwaukee Journal Sentinel/MedPage Today, *Follow the Money: Pain, Policy, and Profit*, Feb. 19, 2012, *available at* at http://medpagetoday.com/Neurology/PainManagement/31256.
[201] Chaudhy Letter, *supra*, at 5.

School of Medicine and Public Health, was at the center of the investigation.[202]

148. The Senate Finance Committee asked for any grants or financial transfers used to produce the book, the revenue generated from the sale of the book, each state that distributed the book, and the names of any people or organization involved in writing or editing the book.[203]

149. Within days, APF's board voted to dissolve the organization and it ceased to exist. The FSMB responded to the Senate Finance Committee's inquiry, however, and agreed that "the abuse and misuse of opioids is a serious national problem."[204] Dr. Chaudhy, speaking on behalf of the FSMB, acknowledged that "prescription drug abuse and related deaths has grown at an alarming pace in the United States."[205] Dr. Chaudhy described Dr. Fishman, the author of *Opioid Prescribing*, as "one of the nation's leading experts in pain medicine."[206]

150. *Opioid Prescribing* was released from 2007 through January 2012, was distributed in each of the 50 states, including Texas, and supported in the medical community as an educational resource for doctors.[207] The book is still being sold today. For example, a used copy of the book is being sold on Amazon.com by Delta River Books, located in Texas, for $51.49 plus $3.99 in shipping. Dr. Fishman also toured and gave keynote speeches about *Opioid Prescribing*. For example, Dr. Fishman presented the keynote at the Federation of State Medical Board Meeting in Fort Worth, Texas on April 28, 2012, which lasted three days.[208] The book was also used extensively by state regulators to make safe and responsible decisions about prescribing opioids.[209]

---

[202] Chaudhy Letter, *supra*.
[203] *Id.* at 3.
[204] Letter to Max Baucus and Charles Grassley dated June 8, 2012 from Humayun J. Chaudhy, DO, FACP, at 1.
[205] Chaudhy Letter, *supra*, at 1.
[206] *Id.* at 5.
[207] *Id.*
[208] U.C. Davis, *Fishman Gives Keynote at Federation of State Medical Boards Meeting*, May 1, 2012, *available at* https://ucdmc.ucdavis.edu/publish/news/newsroom/6523.
[209] Chaudhy, *supra*, at 5, 17.

151. As described herein, Dr. Fishman and his book was partly funded by Endo and Purdue, among others as evidenced in the response. In 2004, Purdue paid $87,895 in the form of a grant to the FSMB to update the FSMB *Model Guidelines for the Use of Controlled Substances in the Treatment of Pain*, along with other objectives related to opioids.[210] In 2005, Purdue paid $244,000 to FSMB and in 2006, Purdue paid $207,000 to FSMB for the continuation of the same project.[211] In 2008, Endo and Purdue each paid $100,000 in the form of a grant for the distribution of *Responsible Opioid Prescribing*.[212] Thus, from 2000-2012, Purdue paid $734,505.06 and Endo paid $411,620.00 to the FSMB and FSMB Foundation.

152. Dr. Chaudhy's response merely underscored Defendants' role, through KOLs and Front Groups, in controlling the message these groups conveyed about opioids.

2. American Academy of Pain Medicine ("AAPM")

153. The American Academy of Pain Medicine, with Defendants' assistance, prompting, involvement, and funding, issued treatment guidelines and sponsored and hosted medical education programs essential to Defendants' deceptive marketing of chronic opioid therapy.

154. AAPM received over $2.2 million in funding since 2009 from opioid manufacturers. AAPM maintained a corporate relations council, whose members paid $25,000 per year (on top of other funding) to participate. The benefits included allowing members to present educational programs at off-site dinner symposia in connection with AAPM's marquee event – its annual meeting held in Palm Springs, California, or other resort locations. AAPM describes the annual event as an "exclusive venue" for offering education programs to doctors. Membership in the corporate relations council also allows drug company executives and marketing staff to meet

[210] Chaudhy Letter, *supra*, at 11.
[211] *Id.* at 11-12.
[212] *Id.* at 12.

with AAPM executive committee members in small settings. Defendants Endo, and Purdue were members of the council and presented deceptive programs to doctors who attended this annual event.

155. AAPM is viewed internally by Endo as "industry friendly," with Endo advisors and speakers among its active members. Endo attended AAPM conferences, funded its CMEs, and distributed its publications. The conferences sponsored by AAPM heavily emphasized sessions on opioids – 37 out of roughly 40 at one conference alone. AAPM's presidents have included top industry-supported KOLs Perry Fine, Russell Portenoy, and Lynn Webster. Dr. Webster was even elected president of AAPM while under a DEA investigation. Another past AAPM president, Dr. Scott Fishman, stated that he would place the organization "at the forefront" of teaching that "the risks of addiction are . . . small and can be managed."[213]

156. Defendants influenced AAPM through both their significant and regular funding and the leadership of pro-opioid KOLs within the organization. AAPM's staff understood they and their industry funders were engaged in a common task – propagate a "pain epidemic" and solve it by teaching that opioids were safe and effective for treating chronic pain.

157. In 1997, AAPM and the American Pain Society jointly issued a consensus statement, *The Use of Opioids for the Treatment of Chronic Pain*, which endorsed opioids to treat chronic pain and claimed there was a low risk that patients would become addicted to opioids. The co-author of the statement, Dr. Haddox, was a paid speaker for Purdue at the time. Dr. Portenoy, Defendants' KOL, was the sole consultant. The consensus statement remained on AAPM's website until 2011.

---

[213] Interview by Paula Moyer with Scott M. Fishman, M.D., Professor of Anesthesiology and Pain Medicine, Chief of the Division of Pain Medicine, Univ. of Cal., Davis (2005), *available at* http://www.medscape.org/viewarticle/500829.

158. AAPM and APS issued their own guidelines in 2009 ("AAPM/APS Guidelines") and continued to recommend using opioids to treat chronic pain. Fourteen of the 21 panel members who drafted the AAPM/APS Guidelines, including KOLs Dr. Portenoy and Dr. Perry Fine of the University of Utah, received support from Janssen, Endo, and Purdue.

159. The 2009 Guidelines promote opioids as "safe and effective" for treating chronic pain, despite acknowledging limited evidence, and conclude that the risk of addiction is manageable for patients regardless of past abuse histories. One panel member, Dr. Joel Saper, Clinical Professor of Neurology at Michigan State University and founder of the Michigan Headache & Neurological Institute, resigned from the panel because he was concerned the 2009 Guidelines were influenced by contributions that drug companies, including Defendants, made to the sponsoring organizations and committee members. These AAPM/APS Guidelines have been a particularly effective channel of deception and have influenced not only treating physicians, but also the body of scientific evidence on opioids. The Guidelines have been cited 732 times in academic literature, were disseminated in and around Newton County during the relevant time period, are still available online, and were reprinted in the *Journal of Pain*.

B. Defendants' Marketing Scheme Misrepresented the Risks and Benefits of Opioids.

160. To convince doctors and patients in Newton County that opioids can and should be used to treat chronic pain, Defendants had to convince them that long-term opioid use is non-addictive, safe, and effective. Knowing they could do so only by deceiving those doctors and patients about the risks and benefits of long-term opioid use, Defendants made claims that were not supported by, and were contrary to, the scientific evidence. Defendants have not corrected their misrepresentations.

161. Defendants also deceptively trivialized and failed to disclose the risks of long-term opioid use, particularly the risks of addiction and overdose, through a series of misrepresentations that have since been conclusively debunked by numerous published studies and the magnitude of human misery caused by Defendants' deceptions. These misrepresentations – which are described below – reinforced each other and created the dangerously misleading impression that opioids are the best treatment option for any recurrent moderate pain because: (1) only a miniscule number of patients, if any, would become addicted; (2) all patients with a substantial risk of becoming addicted to opioids could be readily identified; (3) patients who displayed signs of addiction probably were not addicted and, in any event, could easily be weaned from the drugs; (4) the use of higher opioid doses do not escalate risk of addiction or overdose; and (5) "abuse-deterrent" opioids are reliably safe and effective for perpetual use. Defendants still espouse these misrepresentations today.

162. ***First***, Defendants falsely claimed the risk of addiction is low and unlikely to develop when opioids are prescribed, as opposed to those obtained illicitly; and failed to disclose the greater risk of addiction with prolonged use of opioids.[214] For example:

a) Purdue sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which instructed that addiction is rare and limited to extreme cases of unauthorized dose escalations, obtaining duplicative opioid prescriptions from multiple sources, or theft. This publication is still available online;

b) Endo sponsored a website, Painknowledge.com, which claimed in 2009 that "[p]eople who take opioids as prescribed usually do not become addicted." Another Endo website, PainAction.com, stated "Did you know? Most chronic pain patients do not become addicted to the opioid medications that are prescribed for them.";

c) Endo distributed a pamphlet with the Endo logo entitled *Living with Someone with Chronic Pain*, which stated that: "Most health care providers

[214] *See, e.g.*, Manchikanti, Ex. A, at 22 (blaming adverse consequences on abuses and overuses instead of appropriately blaming opioids used as directed).

who treat people with pain agree that most people do not develop an addiction problem." A similar statement appeared on the Endo website, www.opana.com;

d) Janssen reviewed, edited, approved, and distributed a patient education guide entitled *Finding Relief: Pain Management for Older Adults* (2009), which described as "myth" the claim that opioids are addictive, and asserted as fact that "[m]any studies show that opioids are rarely addictive when used properly for the management of chronic pain.";

e) Janssen currently runs a website, Prescriberesponsibly.com (last updated July 2, 2015), which claims that concerns about opioid addiction are "overestimated";

f) Purdue sponsored APF's *A Policymaker's Guide to Understanding Pain & Its Management* – which claims that less than 1% of children prescribed opioids will become addicted and that pain is undertreated due to "misconceptions about opioid addiction[]." This publication is still available online; and

g) Detailers for Purdue, Endo, and Janssen in and around Newton County minimized or omitted any discussion with doctors of the risk of addiction; misrepresented the potential for opioid abuse with purportedly abuse-deterrent formulations; and routinely did not correct the misrepresentations noted above.

163. These claims contradict empirical evidence. As noted by the CDC, there is "extensive evidence" of the "possible harms of opioids (including opioid use disorder [an alternative term for opioid addiction])."[215] The CDC has explained that "[o]pioid pain medication use presents serious risks, including...opioid use disorder" and that "continuing opioid therapy for 3 months substantially increases risk for opioid use disorder."[216] In fact, as many as "1 in 4 patients receiving long-term opioid therapy in primary care settings struggle with opioid use disorder."[217] Among the 12 recommendations by the new CDC guidelines to improve patient care and safety is that non-opioid therapy is preferred for chronic pain unless there is active cancer or it is for palliative

[215] Centers for Disease Control and Prevention, *CDC Guideline for Prescribing Opioids for Chronic Pain – United States 2016*, Mar. 18, 2016.
[216] *Id.*
[217] *Id.*

and end-of-life care.[218]

164. Defendants' long-standing claims that opioid addiction and overdose are anomalies largely attributable to patient abuse of the drug, are demonstrably false. Indeed, the majority of cases "involving injury and death occur in people using opioids ***exactly*** as prescribed . . ."[219]

165. In 2010, a study addressed the rates of opioid overdose with patients receiving average prescribed daily opioids versus patients receiving medically prescribed chronic opioid therapy.[220] The patients included those receiving three-plus opioid prescriptions within 90-days for chronic non-cancer pain between 1997 and 2005.[221] Patients who received 50-99 mg had a 3.7-fold increase in overdose risk (95% C.I. 1.5, 9.5) and a 0.7 annual overdose rate.[222]

166. The authors determined that even though opioids provide some pain relief for chronic pain, balancing the long-term risks with the benefits was still "poorly understood."[223] Those patients who had not received opioids lately had a lower risk of overdose, however, than patients consistently receiving opioids at a low dosage.[224]

167. The authors pointed to previous studies that indicated a rise in opioid-related overdoses with an increase in prescribing opioids for non-cancer pain, but the belief that such phenomenon was caused by patients obtaining opioids from non-medical sources.[225] This study, proves for the first time, however, that the risk of overdose is directly linked to the prescription and use of medically prescribed opioids.[226]

---

[218] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[219] Manchikanti, Ex. A, at 22.
[220] Kate M. Dunn, Ph.D., Kathleen W. Saunders, J.D., *Overdose and Prescribed Opioids: Association among Chronic Non-Cancer Pain Patients*, Ann. Intern. Med., Dec. 10, 2010, at 2.
[221] *Id.*
[222] *Id.*
[223] *Id.*
[224] Dunn, *supra*, at 6.
[225] *Id.* at 7.
[226] *Id.*

168. The authors of a Washington study in which the authors obtained Washington Medicaid data from the Washington Heath Care Authority reached a similar conclusion.[227] The opioid prescription claim history was examined for each "opioid poisoning" for the months that enrollees received Medicaid FFS prescription benefits.[228] The authors concluded that a large percentage of opioid poisonings happened at lower prescribed doses and in individuals who were not considered chronic users.[229]

169. The authors noted that previous opioid guidelines focused on opioid doses above 80-120 mg/d MED even though previous studies showed risk of opioid deaths and poisonings at much lower doses and that most non-methadone opioid poisonings had been prescribed below these guidelines levels.[230] The authors concluded that only a small percentage of patients are prescribed opioids at a dosage greater than 120 mg/d MED, but that a large percentage of the opioids poisonings have been occurring in patients taking lower doses and in patients not considered chronic users.[231] Overdoses were therefore occurring in patients prescribed opioids for chronic non-cancer pain at increased rates and the overdose risk increased with an average prescription dose.[232] The guidelines and other educational material regarding opioids need to be changed to reflect the opioid poisoning among this population.[233]

170. In fact, "[t]he majority of deaths (60%) occur in patients when they are given prescriptions based on prescribing guidelines by medical boards with 20% of deaths in low dose opioid therapy . . . ."[234] The way to cure the "crisis of opioid use in the United States" is to change

---

[227] Deborah Fulton-Kehoe, Ph.D., *Opioid Poisonings in Washington State Medicaid: Trends, Dosing, and Guidelines*, 53 Medical Care 8, Aug. 2015, at 680.
[228] *Id.*
[229] *Id.*
[230] *Id.* at 683.
[231] *Id.* at 684.
[232] *Id.*
[233] *Id.*
[234] Manchikanti, Ex. A, at 1.

"inappropriate prescribing patterns, which are largely based on a lack of knowledge, perceived safety, and inaccurate belief of undertreatment of pain."[235]

171. Another study found that approximately 60% of overdoses occur in medical users of opioids prescribed by a single physician to manage chronic pain.[236] Non-medical users comprise only a statistical minority of opioid overdoses.[237]

172. Scientific evidence underscores the conclusion that low-dose opioid therapy for chronic pain, opioids taken as prescribed, opioids obtained from a single doctor, and opioids prescribed pursuant to prescribing guidelines cause many overdoses. Defendants, however, disseminated contrary messaging throughout their marketing campaigns to sell more opioids.

173. ***Second***, Defendants falsely instructed doctors and patients that signs of addiction are actually signs of undertreated pain and should be treated by prescribing more opioids. Defendants called this phenomenon "pseudoaddiction" – a term coined by Dr. David Haddox, who went to work for Purdue, and popularized by Dr. Russell Portenoy, a KOL for Endo, Janssen, and Purdue – and claimed that pseudoaddiction is substantiated by scientific evidence. For example:

a) Purdue sponsored *Responsible Opioid Prescribing* (2007), which taught that behaviors such as "requesting drugs by name," "demanding or manipulative behavior," seeing more than one doctor to obtain opioids, and hoarding, are all signs of pseudoaddiction, rather than true addiction. *Responsible Opioid Prescribing* remains for sale online. The 2012 edition continues to teach that pseudoaddiction is real;

b) Janssen sponsored, funded, and edited the *Let's Talk Pain* website, which in 2009 stated: "pseudoaddiction . . . refers to patient behaviors that may occur when pain is under-treated . . . . Pseudoaddiction is different from true addiction because such behaviors can be resolved with effective pain management.";

---

[235] Manchikanti, Ex. A, at 1.
[236] Barbara Zedler, M.D., *Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose Among Veterans Health Administration Patients*, Pain Medicine, 2014, at 1912, attached hereto as Exhibit F.
[237] *Id.*

c) Endo sponsored a National Initiative on Pain Control (NIPC) CME program in 2009 titled *Chronic Opioid Therapy: Understanding Risk While Maximizing Analgesia*, which promoted pseudoaddiction by teaching that a patient's aberrant behavior was the result of untreated pain. Endo substantially controlled NIPC by funding NIPC projects; developing, specifying, and reviewing content; and distributing NIPC materials;

d) Purdue published a pamphlet in 2011 entitled *Providing Relief, Preventing Abuse*, which described pseudoaddiction as a concept that "emerged in the literature" to describe the inaccurate interpretation of [drug-seeking behaviors] in patients who have pain that has not been effectively treated."; and

e) Purdue sponsored a CME program entitled *Path of the Patient, Managing Chronic Pain in Younger Adults at Risk for Abuse*. In a role play, a chronic pain patient with a history of drug abuse tells his doctor that he is taking twice as many hydrocodone pills as directed. The narrator notes that because of pseudoaddiction, the doctor should not assume the patient is addicted even if he persistently asks for a specific drug, seems desperate, hoards medicine, or "overindulges in unapproved escalating doses." The doctor treats this patient by prescribing a high-dose, long-acting opioid.

174. The 2016 CDC Guideline rejects the concept of pseudoaddiction. The CDC Guideline nowhere recommends that opioid dosages be increased if a patient is not experiencing pain relief. To the contrary, the Guideline explains that "[p]atients who do not experience clinically meaningful pain relief early in treatment...are unlikely to experience pain relief with longer-term use,"[238] and that physicians should "reassess[] pain and function within 1 month"[239] in order to decide whether to "minimize risks of long-term opioid use by discontinuing opioids"[240] because the patient is "not receiving a clear benefit."[241]

175. ***Third,*** Defendants falsely instructed doctors and patients that addiction risk screening tools, patient contracts, urine drug screens, and similar strategies allowed them to

[238] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[239] *Id.*
[240] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[241] *Id.*

reliably identify and safely prescribe opioids to patients predisposed to addiction. These misrepresentations were especially insidious because Defendants aimed them at general practitioners and family doctors who lack the time and expertise to closely manage higher-risk patients. Defendants' misrepresentations made these doctors feel more comfortable prescribing opioids to their patients, and patients more comfortable starting opioid therapy for chronic pain. For example:

a) Endo paid for a 2007 supplement in the *Journal of Family Practice* written by a doctor who became a member of Endo's speakers' bureau in 2010. The supplement, entitled *Pain Management Dilemmas in Primary Care: Use of Opioids*, emphasized the effectiveness of screening tools, claiming that patients at high risk of addiction could safely receive chronic opioid therapy using a "maximally structured approach" involving toxicology screens and pill counts;

b) Purdue sponsored a 2011 webinar, *Managing Patient's Opioid Use: Balancing the Need and Risk*, which claimed that screening tools, urine tests, and patient agreements prevent "overuse of prescriptions" and "overdose deaths;" and

c) As recently as 2015, Purdue has represented in scientific conferences that "bad apple" patients – and not opioids – are the source of the addiction crisis and that once those "bad apples" are identified, doctors can safely prescribe opioids without causing addiction.

176. Once again, the 2016 CDC Guideline confirms these representations are false. The Guideline notes that there are no studies assessing the effectiveness of risk mitigation strategies – such as screening tools, patient contracts, urine drug testing, or pill counts – widely believed by doctors to detect and deter outcomes related to addiction and overdose.[242] As a result, the Guideline recognizes that doctors should not overestimate the risk screening tools for classifying patients as high or low risk for opioid addiction because they are insufficient to rule out the risks of long-term opioid therapy.[243]

[242] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[243] *Id.*

177. ***Fourth***, to underplay the risk and impact of addiction and make doctors feel more comfortable starting patients on opioids, Defendants falsely claimed that opioid dependence can easily be addressed by tapering and that opioid withdrawal is not a problem thereby failing to disclose the increased difficulty of stopping opioids after long-term use.

178. For example, a CME sponsored by Endo, entitled *Persistent Pain in the Older Adult*, claimed that withdrawal symptoms can be avoided by tapering a patient's opioid dose by 10%-20% for 10 days. And Purdue sponsored APF's *A Policymaker's Guide to Understanding Pain & Its Management*, which claimed that "[s]ymptoms of physical dependence can often be ameliorated by gradually decreasing the dose of medication during discontinuation."

179. Defendants deceptively minimized the significant symptoms of opioid withdrawal, which, as explained in the 2016 CDC Guideline, include drug cravings, anxiety, insomnia, abdominal pain, vomiting, diarrhea, sweating, tremor, tachycardia (rapid heartbeat), spontaneous abortion and premature labor in pregnant women, and the unmasking of anxiety, depression, and addiction – and grossly understated the difficulty of tapering, particularly after long-term opioid use.

180. Yet the 2016 CDC Guideline recognizes that the duration of opioid use and the dosage of opioids prescribed should be limited to "minimize the need to taper opioids to prevent distressing or unpleasant withdrawal symptoms,"[244] because "***physical dependence on opioids is an expected physiologic response in patients exposed to opioids for more than a few days.***"[245] (Emphasis Added.) The Guideline further states that "tapering opioids can be especially challenging after years on high dosages because of physical and psychological dependence"[246] and

[244] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[245] *Id.*
[246] *Id.*

highlights the difficulties, including the need to carefully identify "a taper slow enough to minimize symptoms and signs of opioid withdrawal"[247] and pausing and restarting tapers depending on the patient's response.

181. The CDC also acknowledges the lack of any "high-quality studies comparing the effectiveness of different tapering protocols for use when opioid dosage is reduced or opioids are discontinued."[248] Contrary to the *Treatment Options* distributed by the APF, withdrawal from opioids involves much more than mere "physical" dependence occurring only when opioids are stopped suddenly or the dose lowered too quickly.

182. ***Fifth***, Defendants falsely claimed that doctors and patients could increase opioid dosages indefinitely without added risk and failed to disclose the greater risks to patients at higher dosages. The ability to escalate dosages was critical to Defendants' efforts to market opioids for long-term use to treat chronic pain because, absent this misrepresentation, doctors would have abandoned treatment when patients built up tolerance and lower dosages did not provide pain relief. For example:

a) Purdue sponsored *APF's Treatment Options: A Guide for People Living with Pain* (2007), which claims that some patients "need" a larger dose of an opioid, regardless of the dose currently prescribed. The guide stated that opioids have "no ceiling dose" and are therefore the most appropriate treatment for severe pain. This guide is still available for sale online;

b) Endo sponsored a website, painknowledge.com, which claimed in 2009 that opioid dosages may be increased until "you are on the right dose of medication for your pain.";

c) Endo distributed a pamphlet edited by a KOL entitled *Understanding Your Pain: Taking Oral Opioid Analgesics*, which was available during the time period of this Complaint on Endo's website. In Q&A format, it asked "If I take the opioid now, will it work later when I really need it?" The response is, "The dose can be increased. . . . You won't 'run out' of pain relief.";

[247] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[248] *Id.*

d) Janssen sponsored a patient education guide entitled *Finding Relief: Pain Management for Older Adults* (2009), which was distributed by its sales force. This guide listed dosage limitations as "disadvantages" of other pain medicines but omitted any discussion of risks of increased opioid dosages;

e) Purdue's In the Face of Pain website promotes the notion that if a patient's doctor does not prescribe what, in the patient's view, is a sufficient dosage of opioids, he or she should find another doctor who will;

f) Purdue sponsored APF's *A Policymaker's Guide to Understanding Pain & Its Management*, which taught that dosage escalations are "sometimes necessary," even unlimited ones, but did not disclose the risks from high opioid dosages. This publication is still available online;

g) Purdue sponsored a CME entitled *Overview of Management Options* that is still available for CME credit. The CME was edited by a KOL and taught that NSAIDs and other drugs, but not opioids, are unsafe at high dosages; and

h) Purdue presented a 2015 paper at the College on the Problems of Drug Dependence, the "the oldest and largest organization in the US dedicated to advancing a scientific approach to substance use and addictive disorders," challenging the correlation between opioid dosage and overdose.

183. These claims conflict with the scientific evidence, as confirmed by the FDA and CDC. As the CDC explains in its 2016 Guideline, the "[b]enefits of high-dose opioids for chronic pain are not established"[249] while the "risks for serious harms related to opioid therapy increase at higher opioid dosage."[250]

184. More specifically, the CDC explains, "there is now an established body of scientific evidence showing that overdose risk is increased at higher opioid dosages."[251] Similarly, there is an "increased risk for opioid use disorder, respiratory depression, and death at higher dosages."[252] That is why the CDC advises doctors to avoid increasing dosages above 90 morphine milligram equivalents per day.

---

[249] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[250] *Id.*
[251] *Id.*
[252] *Id.*

185. ***Finally***, Defendants' deceptive marketing of the so-called abuse-deterrent properties of some of their opioids has created false impressions that these opioids reliably curb addiction and abuse.

186. More specifically, Defendants have made misleading claims about the ability of their so-called abuse-deterrent opioid formulations to deter use. For example, Endo's advertisements for the 2012 reformulation of Opana ER claimed that it was designed to be crush resistant in a way that suggested it was more difficult to misuse the product. This claim was false.

187. The FDA warned in a 2013 letter that there was no evidence Endo's design would provide a reduction in oral, intranasal or intravenous use.[253] Moreover, Endo's own studies, which it failed to disclose, showed that Opana ER could still be ground and chewed.

188. In a 2016 settlement with the State of New York, Endo agreed not to make statements in New York that Opana ER was designed to be or is crush-resistant. The State found those statements false and deceptive because there was no difference in the ability to extract the narcotic from Opana ER.

189. Similarly, the 2016 CDC Guideline states that no studies support the notion that "abuse-deterrent technologies [are] a risk mitigation strategy for deterring or preventing abuse,"[254] noting that the technologies – even when they work – "do not prevent opioid abuse through oral intake, the most common route of opioid abuse, and can still be abused by non-oral routes."[255]

190. These numerous, long-standing misrepresentations of the risks of long-term opioid use spread by Defendants successfully convinced doctors and patients to underestimate those risks.

---

[253] *See FDA Statement: Original Opana ER Relisting Determination*, May 10, 2013.
[254] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[255] *Id.*

C. Defendants Grossly Overstated the Benefits of Chronic Opioid Therapy.

191. To convince doctors and patients that opioids should be used to treat chronic pain, Defendants had to persuade them that there was a significant benefit to long-term opioid use. But as the 2016 CDC Guideline makes clear, there is "insufficient evidence to determine the long-term benefits of opioid therapy for chronic pain."[256]

192. In fact, the CDC found no evidence showing "a long-term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized trials ≤ 6 weeks in duration)"[257] and that other treatments were more or equally beneficial and less harmful than long-term opioid use.

193. Nonetheless, Defendants were legion in their misrepresentations that opioid drugs were appropriate for use as a long-term lifestyle. For example:

a) Endo distributed advertisements that claimed that the use of Opana ER for chronic pain would allow patients to perform demanding tasks like construction work or work as a chef and portrayed seemingly healthy, unimpaired subjects;

b) Janssen sponsored and edited a patient education guide entitled *Finding Relief: Pain Management for Older Adults* (2009) – which states as "a fact" that "opioids may make it easier for people to live normally." The guide lists expected functional improvements from opioid use, including sleeping through the night, returning to work, recreation, sex, walking, and climbing stairs;

c) Purdue ran a series of advertisements for OxyContin in 2012 in medical journals entitled "pain vignettes," which were case studies featuring patients with pain conditions persisting over several months and recommending OxyContin for them. The ads implied that OxyContin improves patients' function;

d) *Responsible Opioid Prescribing* (2007), sponsored and distributed by Endo and Purdue, taught that relief of pain by opioids, by itself, improved patients' function. The book remains for sale online;

---

[256] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[257] *Id.*

e) Purdue sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which counseled patients that opioids "give [pain patients] a quality of life we deserve." The guide was available online until APF shut its doors in 2012;

f) Endo's NIPC website *painknowledge.com* claimed in 2009 that with opioids, "your level of function should improve; you may find you are now able to participate in activities of daily living, such as work and hobbies, that you were not able to enjoy when your pain was worse." Elsewhere, the website promoted improved quality of life (as well as "improved function") as benefits of opioid therapy. The grant request that Endo approved for this project specifically indicated NIPC's intent to make misleading claims about function, and Endo closely tracked visits to the site;

g) Endo was the sole sponsor, through NIPC, of a series of CMEs titled *Persistent Pain in the Older Patient*, which claimed that chronic opioid therapy has been "shown to reduce pain and improve depressive symptoms and cognitive functioning." The CME was disseminated via webcast;

h) Janssen sponsored, funded, and edited a website, *Let's Talk Pain*, in 2009, which featured an interview edited by Janssen claiming that opioids allowed a patient to "continue to function." This video is still available today on YouTube;

i) Purdue sponsored the development and distribution of APF's *A Policymaker's Guide to Understanding Pain & Its Management*, which claimed that "multiple clinical studies" have shown that opioids are effective in improving daily function, psychological health, and health-related quality of life for chronic pain patients." The Policymaker's Guide was originally published in 2011 and is still available online today; and

j) Purdue's, Endo's, and Janssen's sales representatives have conveyed and continue to convey the message that opioids will improve patient function.

194. These claims are unsupported by the scientific literature. The 2016 CDC Guideline explained, "There is no good evidence that opioids improve pain or function with long-term use"[258] and "complete relief of pain is unlikely."[259] The CDC reinforced this conclusion throughout its 2016 Guideline:

a) "No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least 1 year

[258] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[259] *Id.* (emphasis added).

later . . . .";[260]

b) "Although opioids can reduce pain during short-term use, the clinical evidence review found insufficient evidence to determine whether pain relief is sustained and whether function or quality of life improves with long-term opioid therapy.";[261] and

c) "[E]vidence is limited or insufficient for improved pain or function with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as low back pain, headache, and fibromyalgia."[262]

195. The CDC also noted that the risks of addiction and death "can cause distress and inability to fulfill major role obligations."[263]

196. Defendants also falsely emphasized or exaggerated the risks of competing products like NSAIDs so that doctors and patients would look to opioids first for treating chronic pain. Once again, Defendants' misrepresentations contradicted non-industry sponsored scientific evidence. In addition, Purdue misleadingly promoted OxyContin as unique among opioids in providing 12 continuous hours of pain relief with one dose. In fact, OxyContin does not last for 12 hours – a fact that Purdue has known at all times relevant to this action.

197. According to Purdue's own research, OxyContin wears off in under six hours in one quarter of patients and in under 10 hours in more than half. The reason is that OxyContin tablets release approximately 40% of their active medicine immediately, after which release tapers. Although the patient experiences a powerful initial response, there is little or no pain relief at the end of the dosing period because less medicine is released.

198. This phenomenon is known as "end of dose" failure, and the FDA found in 2008 that a substantial number of chronic pain patients taking OxyContin experience it.

---

[260] *CDC Guidelines for Prescribing Opioids for Chronic Pain, supra.*
[261] *Id.*
[262] *Id.*
[263] *Id.*

199. This "end of dose" failure not only renders Purdue's promise of 12 hours of relief false and deceptive, it also makes OxyContin more dangerous because the declining pain relief patients experience toward the end of each dosing period drives them to take more OxyContin before the next dosing period begins, quickly increasing the amount of drug they are taking and spurring growing dependence.

200. Purdue's competitors were aware of this problem. For example, Endo ran advertisements for Opana ER referring to "real" 12-hour dosing. Nevertheless, Purdue falsely promoted OxyContin as if it were effective for a full 12 hours. Indeed, Purdue's sales representatives continue to tell doctors in and around Newton County that OxyContin lasts a full 12 hours.

D. Defendants also engaged in Other Unlawful, Unfair, and Fraudulent Misconduct.

201. Other Defendants herein participated in illicit and unlawful prescribing of its drugs. For example, Purdue did not report illegal prescribing of OxyContin until years after law enforcement shut down a Los Angeles clinic that prescribed more than 1.1 million OxyContin tablets. In doing so, Purdue protected its own profits at the expense of public health and safety.

202. The State of New York also found that Endo failed to require sales representatives to report signs of addiction, diversion, and inappropriate prescribing; paid bonuses to sales representatives for detailing prescribers who were subsequently arrested or convicted for illegal prescribing; and failed to prevent sales representatives from visiting prescribers whose suspicious conduct had caused them to be placed on a no-call list.

E. Defendants Targeted Susceptible Prescribers and Vulnerable Patient Populations.

203. As part of their deceptive marketing scheme, Defendants identified and targeted susceptible prescribers and vulnerable patient populations in the U.S. and in and around Newton

County. For example, Defendants focused their deceptive marketing on primary care doctors, who were more likely to treat chronic pain patients and prescribe opioids, but were less likely to be educated about treating pain and the risks and benefits of opioids.

204. Defendants also targeted vulnerable patient populations like the elderly and veterans, who tend to suffer from chronic pain. Defendants targeted these vulnerable patients even though the risks of long-term opioid use were significantly greater for them.

205. For example, the 2016 CDC Guideline observes that existing evidence shows that elderly patients taking opioids suffer from elevated fall and fracture risks, greater risk of hospitalization, and increased vulnerability to adverse drug effects and interactions. The Guideline therefore concludes that there are "special risks of long-term opioid use for elderly patients" and recommends that doctors use "additional caution and increased monitoring" to minimize the risks of opioid use in elderly patients.

206. The same is true for veterans, who are more likely to use anti-anxiety drugs (benzodiazepines) for post-traumatic stress disorder, which interact dangerously with opioids.

207. Defendants achieved their goal in targeting these vulnerable populations when the Arthritis Foundation published its *Guide to Pain Management* in 2003 ("*Pain Management Guide*").[264] The *Pain Management Guide* was published by a neutral third-party that not only believed the message Defendants had been selling for years, but it continued to relay that message to patients experiencing chronic pain – elderly patients with arthritis.[265]

208. The *Pain Management Guide* was intended for a population of "70 million Americans who have arthritis or other related diseases."[266] It parroted falsities, such as the low risk

[264] Susan Bernstein, *The Arthritis Foundation's Guide to Pain Management*, Arthritis Foundation, 2003.
[265] *Id.*
[266] *Id.*

of developing an addiction to opioids and cited Defendants' false statistic: "The addiction rate from narcotics is approximately one percent."[267]

209. The Arthritis Foundation even accepted and repeated Defendants' distinction between dependence and addiction. A person with dependence suggests he or she would experience withdrawal symptoms upon stopping opioids while addiction "is a self-destructive, habitual use" of opioids.[268] The *Pain Management Guide* brushes aside concerns about addiction and recommends higher doses of opioids for patients who develop a dependence on opioids[269] – the exact message that Defendants had been spouting for years.

210. The fact that neutral third parties were relying on and buying Defendants' false propositions only verifies Defendants' successful fraud on the medical and non-medical community at large.

F. Although Defendants knew that their Marketing of Opioids was False and Deceptive, they Fraudulently Concealed their Misconduct.

211. Defendants, both individually and collectively, made, promoted, and profited from their misrepresentations about the risks and benefits of opioids for chronic pain even though they knew their misrepresentations were false and deceptive. Defendants knew that the marketing scheme being promoted by Defendants was misleading, inaccurate, and simply false. The history of opioids, as well as research and clinical experience over the last 20 years, established that opioids were highly addictive and responsible for a long list of very serious adverse outcomes.

212. In The Journal of the American Medical Association November 2002 edition, which Defendants meant to reach physicians throughout the nation, Purdue advertised OxyContin

[267] Bernstein, *supra*, at 70-71.
[268] *Id.* at 70.
[269] *Id.*

as a safe drug with minimal safety risks.[270] The ad depicts a man and boy fishing with a title in large white letters exclaiming that "THERE CAN BE LIFE WITH RELIEF" with "LIFE WITH RELIEF" as the largest words in the advertisement.[271] Purdue then informs physicians that "[t]he most serious risk associated with opioids, including OxyContin, is respiratory depression."[272]

213. Purdue fraudulently represented that respiratory depression was not only the most serious risk for its own drug OxyContin, but for opioids in general, even though it knew that opioids carried a risk of addiction and death.

214. The ad continues with benign side effects that may occur with the use of OxyContin, such as "constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness."[273] These side effects are certainly a far cry from addiction or death. Of course this ad also claims that OxyContin is a "continuous around-the-clock analgesic," which is equally false.[274]

215. Because of the bold misrepresentations and omissions in its ads occurring in the October 2, 2002 JAMA issue, and one occurring in the November 13, 2002 issue, the FDA wrote a warning letter to Michael Friedman, the Executive Vice President and Chief Operating Officer of Purdue.[275] Mr. Abrams explained that "[y]our journal advertisements omit and minimize the serious safety risks associated with OxyContin, and promote it for uses beyond which have been proven safe and effective."[276] Mr. Abrams reprimanded Purdue for failing to present "any information" in the advertisement about the "potentially fatal risks" or the potential for abuse

---

[270] The Journal of American Medical Association, Nov. 13, 2002.
[271] *Id.* at 1, 3.
[272] *Id.*
[273] *Id.*
[274] JAMA, *supra*, at 1, 3.
[275] Warning Letter from Thomas Abrams, Dir., FDA Div. of Mktg., Adver., & Comme'ns, to Michael Friedman, Exec. Vice Pres. and COO, Purdue Pharma L.P.
[276] *Id.* at 1.

associated with OxyContin.[277]

216. Mr. Abrams was concerned that these advertisements suggested such a "broad use of [OxyContin] to treat pain without disclosing the potential for abuse with the drug and the serious, potentially fatal risks associated with its use. . . ."[278] Purdue's actions were "especially egregious and alarming" given "its potential impact on the public health."[279] Mr. Abrams pointed out to Purdue the reality that "[i]t is particularly disturbing that your November Ad would tout 'Life with Relief,' yet fail to warn that patients can die from taking OxyContin."[280]

217. Purdue Pharma has consistently disregarded serious harm that it knew Oxycontin caused. For example, in Kentucky in 2001, three people and one estate sued Purdue for becoming addicted to OxyContin even though they were taking the drug as prescribed.[281] Several similar lawsuits were filed against Purdue by individuals.[282] Dr. J. David Haddox, an executive at Purdue, responded to these claims: "A lot of these people say, 'Well, I was taking the medicine like my doctor told me to,' and then they start taking more and more and more . . . I don't see where that's my problem."[283]

218. Not surprisingly, three current and former executives from Purdue plead guilty in 2007 to criminal charges that they misled regulators, doctors, and patients about OxyContin's risk of addiction.[284] In pleading guilty to misbranding charges, Purdue admitted it had fraudulently marketed OxyContin as a drug less prone to addiction and as having fewer side effects than other

---

[277] Warning Letter from Thomas Abrams, *supra.*
[278] *Id.* at 2.
[279] *Id.*
[280] *Id.* at 4.
[281] Chris Kahn, *Maker of OxyContin Faces at least 13 Lawsuits,"* July 27, 2001, Port Arthur News.
[282] *Id.*
[283] *Id.*
[284] *See* Barry Meier, *In Guilty Plea, OxyContin Maker to Pay $600 Million,* May 10, 2007, *available at* http://www.nytimes.com/2007/05/10/business/11drug-web.html; *see also* Zee, Ex. B, at 3-4.

opioids.[285] In reality, unlike most other opioids, OxyContin contained pure oxycodone without any other ingredients, which made it a higher-dose narcotic despite its time-release design that Purdue hawked as ameliorating its addictive potential.[286]

219. Defendants avoided detection of their fraudulent conduct by disguising their role in the deceptive marketing through funding and using third parties, such as Front Groups and KOLs. Doctors and patients trusted these third parties and did not realize that it was the pharmaceutical companies that were actually feeding them false and misleading information.

220. Defendants also manipulated their promotional materials and the scientific literature to make it appear that the information promoted was accurate, truthful, and supported by objective evidence when it was not.

221. Thus, Defendants successfully concealed from the medical community and patients facts sufficient to arouse suspicion of the claims Newton County now asserts. Newton County did not know of the existence or scope of Defendants' industry-wide fraud and could not have acquired such knowledge earlier through the exercise of reasonable diligence.

G. By Increasing Opioid Prescriptions and Use, Defendants' Deceptive Marketing Scheme has fueled the Opioid Epidemic and Damaged Newton County Communities.

222. Defendants' misrepresentations deceived doctors and patients about the risks and benefits of long-term opioid use. Studies reveal that many doctors and patients are unaware of or do not understand the risks or benefits of opioids. Indeed, patients often report that they were not warned they might become addicted to opioids prescribed to them. As reported in January 2016, a 2015 survey of more than 1,000 opioid patients found that 4 out of 10 were not told opioids were

[285] *See* Meier, *supra.*
[286] *See id.*

potentially addictive.[287]

223. Defendants' deceptive marketing scheme caused, and continues to cause, doctors in and around Newton County to prescribe opioids for chronic pain conditions such as back pain, headaches, arthritis, and fibromyalgia. Absent Defendants' fraud, these doctors would not have prescribed as many opioids that negatively impacted residents of Newton County.

224. Defendants' deceptive marketing scheme also caused, and continues to cause, patients to purchase and use opioids for their chronic pain believing they are safe and effective. Absent Defendants' deceptive marketing scheme, fewer patients would be using opioids long-term to treat chronic pain, and those patients using opioids would be using less of them.

225. Defendants' deceptive marketing has caused and continues to cause the prescription and use of opioids to explode. Indeed, this dramatic increase in opioid prescriptions and use corresponds with the dramatic increase in Defendants' spending on their deceptive marketing scheme. Defendants' spending on opioid marketing totaled approximately $91 million in 2000. By 2011, that spending had tripled to $288 million.

226. The escalating number of opioid prescriptions written by doctors who were deceived by Defendants' deceptive marketing scheme is the cause of a correspondingly dramatic increase in opioid addiction, overdose, and death throughout the U.S. and Newton County. The increase in opioid prescriptions equals an increase in "disability, medical costs, subsequent surgery, and continued or late opioid use."[288]

227. Scientific evidence demonstrates a strong correlation between opioid prescriptions and addiction to opioids. In a 2016 report, the CDC explained that prescribing opioids has

---

[287] Hazelden Betty Ford Foundation, *Missed Questions. Missed Opportunities*, Jan. 27, 2016, *available at* http://www.hazeldenbettyford.org/about-us/news-and-media/pressrelease/doctors-missing-questions-that-could-prevent-opioid-addiction.
[288] Manchikanti, Ex. A, at 23.

quadrupled since 1999, which has resulted in a parallel increase in opioid overdoses.[289] Indeed, there has been a two-third increase in overdose deaths from using opioids since 2000.[290] For these reasons, the CDC concluded that efforts to rein in the prescribing of opioids for chronic pain are critical "to reverse the cycle of opioid pain medication misuse that contributes to the opioid overdose epidemic."[291]

228. Due to the increase in opioid overdoses, first responders, such as police officers, have been and will continue to be in the position to assist people experiencing opioid-related overdoses.[292] In 2016, "over 1,200 law enforcement departments nationwide carried naloxone in an effort to prevent opioid-related deaths."[293]

229. Defendants' deceptive marketing scheme has also detrimentally impacted children in Newton County. Overprescribing opioids for chronic pain has made the drugs more accessible to school-aged children, who come into contact with opioids after they have been prescribed to friends or relatives in the same household.

230. Defendants' conduct has adversely affected Newton County's child protection agencies in the number of children in foster care driven by parental drug addiction. Children with parents addicted to drugs tend to stay in foster care longer, and they often enter the system having experienced significant trauma, which makes these cases more expensive for counties like Newton County.

---

[289] CDC/NCHS, *National Vital Statistics System, Mortality*, CDC Wonder, Atlanta, GA: US Department of Health and Human Services, 2016, *available at* https://wonder.cdc.gov/; Rudd RA, Seth P, David F, Scholl L, *Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015*, Morb Mortal Wkly Rep., Dec. 16, 2016.
[290] CDC, *National Vital Statistics System, Mortality*, Morb Mortal Wkly Rep., Jan. 1, 2006, at 1378-82, Increases in Drug and Opioid Deaths – United States, 2000-2014.
[291] *CDC Guideline for Prescribing Opioids for Chronic Pain, supra; see also* Rudd, *supra.*
[292] Tex. Att'y Gen. Op. No. KP-0168 (2017).
[293] *Id. citing* http://www.nchrc.org/law-enforcement/us-law-enforcement-who-carry-naloxone/.

231. Opioid addiction is one of the primary reasons that Newton County residents seek treatment for substance dependence. A significant number of admissions for drug addiction were associated with a primary diagnosis of opiate addiction or dependence.

232. Defendants' creation, through false and deceptive advertising and other unlawful and unfair conduct, of a virtually limitless opioid market has significantly harmed Newton County communities. Defendants' success in extending the market for opioids to new patients and chronic pain conditions has created an abundance of drugs available for non-medical and criminal use and fueled a new wave of addiction and injury. It has been estimated that 60% of the opioids to which people are addicted come, directly or indirectly, through doctors' prescriptions.[294]

233. Law enforcement agencies have increasingly associated prescription drug addiction with violent and property crimes. Despite strict federal regulation of prescription drugs, local law enforcement agencies are faced with increasing diversion from legitimate sources for illicit purposes, including doctor shopping, forged prescriptions, falsified pharmacy records, and employees who steal from their place of employment. The opioid epidemic has prompted a growing trend of crimes against pharmacies including robbery and burglary. This ongoing diversion of prescription narcotics creates a lucrative marketplace.

234. The rise in opioid addiction caused by Defendants' deceptive marketing scheme has also resulted in an explosion in heroin use. For example, heroin use has more than doubled in the past decade among adults aged 18 to 25 years.[295] Moreover, heroin-related overdoses in the United States has more than quadrupled since 2010.[296]

---

[294] Nathaniel P. Katz, *Prescription Opioid Abuse: Challenges and Opportunities for Payers*, Am. J. Managed Care, Apr. 19 2013, at 5 ("The most common source of abused [opioids] is, directly or indirectly, by prescription."), *available at* http://www.ajmc.com/publications/issue/2013/2013-1-vol19-n4/Prescription-Opioid-Abuse-Challenges-and-Opportunities-for-Payers.

[295] Centers for Disease Control and Prevention, *Vital Signs: Today's Heroin Epidemic – More People at Risk, Multiple Drugs Abused*, MMWR 2015, *available at* https://www.cdc.gov/vitalsigns/heroin/index.html.

[296] *Id.*

235. The costs and consequences of opioid addiction are staggering. For example, in 2007, the cost of healthcare due to opioid addiction and dependence was estimated at 25 billion, the cost of criminal justice was estimated at 5.1 billion, and the cost of lost workplace productivity was estimated at 25.6 billion.

236. Texas had the second highest healthcare costs in 2015 from opioid abuse in the nation totaling $1.96 billion.[297] One in five Texas high school students has taken prescription drugs without a valid prescription.[298] And four of the top 25 cities for abuse in the United States – two of them located in East Texas – is in Texas.[299]

237. Prescription opioid addiction and overdose have an enormous impact on the health and safety of individuals, as well as communities at large, because the consequences of this epidemic reach far beyond the addicted individual.

238. Newton County has also expended funds for false claims submitted on the County's health plans that were paid as medically necessary when they were not and prescriptions for opioids through worker's compensation benefits.

239. The repercussions for residents of Newton County therefore include job loss, loss of custody of children, physical and mental health problems, homelessness and incarceration, which results in instability in communities often already in economic crisis and contributes to increased demand on community services such as hospitals, courts, child services, treatment centers, and law enforcement. Defendants knew, and should have known, about the harms that their deceptive marketing has caused, and continues to cause, and will cause in the future. Defendants closely monitored their sales and the habits of prescribing doctors. Their sales

---

[297] Craig, *Pandemic*, *supra*.
[298] *Id.*
[299] *Id.*

representatives, who visited doctors and attended CMEs, knew which doctors were receiving their messages and how they were responding.

240. Defendants also had access to and carefully watched government and other data that tracked the explosive rise in opioid use, addiction, injury, and death. Defendants not only knew, but intended that their misrepresentations would persuade doctors to prescribe and encourage patients to use their opioids for chronic pain.

241. Defendants' actions are neither permitted nor excused by the fact that their drug labels may have allowed, or did not exclude, the use of opioids for chronic pain. FDA approval of opioids for certain uses did not give Defendants license to misrepresent the risks and benefits of opioids. Indeed, Defendants' misrepresentations were directly contrary to pronouncements by, and guidance from, the FDA based on the medical evidence and their own labels.

242. Nor is Defendants' causal role broken by the involvement of doctors. Defendants' marketing efforts were ubiquitous and highly persuasive. Their deceptive messages tainted virtually every source doctors could rely on for information and prevented them from making informed decisions. And both doctors and patients in Newton County relied on information Defendants distributed whether it was through ads, magazines, trade journals, websites, CMEs, KOLs, and/or front groups. Defendants also hijacked what doctors wanted to believe – namely, that opioids represented a means of relieving their patients' suffering and of practicing medicine more compassionately.

243. The funds that Newton County has used and will continue to use for all the costs associated with Defendants' false, misleading, and fraudulent marketing are taxpayer funds. Defendants specifically targeted physicians in Newton County with fraudulent claims concerning the benefits of opioids for chronic pain while omitting the lack of efficacy.

244. Defendants also fraudulently omitted the fact that opioids were addictive even though they knew, or should have known, that physicians in Newton County would either use the misinformation Defendants relayed to them to prescribe opioids to Newton County residents or give this information to Newton County residents, resulting in the over-prescribing and/or overuse of opioids in Newton County.

245. Defendants' actions and omissions were each a cause-in-fact of Newton County's past and future damages. Defendants' wrongful conduct caused injuries to Newton County in the past, continues to cause injuries to Newton County, and will continue to cause injuries to Newton County in the future. Future damages include, but are not limited to, additional resources for counseling and medication assisted treatment of addicts, medical treatment for overdoses, life skills training for adolescents, increased law enforcement, and additional resources to treat the psychological effects of opioids and the underlying conditions that make people susceptible to opioid addiction, all of which will be obtained through taxpayer resources.

VII. FIRST CAUSE OF ACTION: NEGLIGENT AND/OR INTENTIONAL CREATION OF A PUBLIC NUISANCE AGAINST ALL DEFENDANTS

246. Newton County re-alleges and incorporates by reference each of the allegations contained in the preceding paragraphs of this Petition as though fully alleged herein.

247. Defendants knowingly encouraged doctors in and around Newton County to prescribe, and residents to use, highly addictive opioids for chronic pain even though Defendants knew using opioids had a high risk of addiction and reduced quality of life.

248. By doing so, Defendants purposefully interfered with Newton County's public health, public safety, public peace, public comfort, and public convenience.

249. Defendants, individually and in concert with each other, have contributed to and/or assisted in creating and maintaining a condition that is harmful to the health and safety of Newton County residents, and/or unreasonably interferes with the peace and comfortable enjoyment of life in violation of Texas law.

250. The public nuisance created by Defendants' actions is substantial and unreasonable – it has caused and continues to cause significant harm to the community – and the harm inflicted outweighs any offsetting benefit.

251. The staggering rates of opioid use resulting from Defendants' marketing efforts have caused, and continues to cause, harm to the community including, but not limited to:

a) Upwards of 30% of all adults use opioids. These high rates of use have led to unnecessary opioid addiction, overdose, injuries, and deaths;

b) Children have been exposed to opioids prescribed to family members or others resulting in injury, addiction, and death. Easy access to prescription opioids has made opioids a recreational drug of choice among Newton County teenagers; opioid use among teenagers is only outpaced by marijuana use. Even infants have been born addicted to opioids due to prenatal exposure causing severe withdrawal symptoms and lasting developmental impacts;

c) Residents of Newton County, who have never taken opioids, have endured both the emotional and financial costs of caring for loved ones addicted to or injured by opioids and the loss of companionship, wages, or other support from family members who have used, become addicted to, overdosed on, or been killed by opioids;

d) More broadly, opioid use and addiction have driven Newton County residents' health care costs higher[300];

e) Employers have lost the value of productive and healthy employees who have suffered from adverse consequences from opioid use;

f) Defendants' success in extending the market for opioids to new patients and chronic conditions has created an abundance of drugs available for criminal

[300] *See, e.g.*, Manchikanti, Ex. A, at 14 (stating that the escalating use of opioids in high doses over long periods of time, lifetime use of long-acting drugs, or the combination has serious consequences for the costs of health care and economic stability).

use and fueled a new wave of addiction and injury. Defendants' scheme created both ends of a new secondary market for opioids – providing both the supply of narcotics to sell and the demand of addicts to buy them;

g) This demand has created additional illicit markets in other opiates, particularly heroin. The low cost of heroin has led some of those who initially become addicted to prescription opioids to migrate to cheaper heroin, fueling a new heroin epidemic in the process;

h) Diverting opioids into secondary, criminal markets and increasing the number of individuals who are addicted to opioids has increased the demands on emergency services and law enforcement in Newton County;

i) All of Defendants' actions have caused significant harm to the community – in lives lost; addictions endured; the creation of an illicit drug market and all its concomitant crime and costs; unrealized economic productivity; and broken families and homes;

j) These harms have taxed the human, medical, public health, law enforcement, and financial resources of Newton County; and

k) Defendants' interference with the comfortable enjoyment of life of a substantial number of people is entirely unreasonable because there is limited social utility to opioid use and any potential value is outweighed by the gravity of harm inflicted by Defendants' actions.

252. Defendants knew, or should have known, that promoting opioid use would create a public nuisance in the following ways:

a) Defendants have engaged in massive production, promotion, and distribution of opioids for use by the citizens of Newton County;

b) Defendants' actions created and expanded the market for opioids, promoting its wide use for pain management;

c) Defendants misrepresented the benefits of opioids for chronic pain and fraudulently concealed, misrepresented, and omitted the serious adverse effects of opioids, including the addictive nature of the drugs; and

d) Defendants knew, or should have known, that their promotion would lead to addiction and other adverse consequences that the larger community would suffer as a result.

253. Defendants' actions were, at the least, a substantial factor in doctors and patients not accurately assessing and weighing the risks and benefits of opioids for chronic pain thereby causing opioids to become widely available and used in Newton County.

254. Without Defendants' actions, opioid use would not have become so widespread and the enormous public health hazard of opioid addiction would not have existed and could have been averted.

255. The health and safety of the citizens of Newton County, including those who use, have used, or will use opioids, as well as those affected by opioid users, is a matter of great public interest and legitimate concern to Newton County's citizens and residents. It was foreseeable to all Defendants that the burden of the opioid crisis would fall to counties like Newton County in the form of social and economic costs. Specifically it was foreseeable that Newton County would sustain damages as an employer obligated to provide healthcare coverage to its employees and as a local government obligated to provide public services to its citizens.

256. The public nuisance created, perpetuated, and maintained by Defendants can be abated and further reoccurrence of such harm and inconvenience can be prevented.

257. Defendants' conduct has affected and continues to affect a considerable number of people within Newton County and is likely to continue to cause significant harm to patients who take opioids, their families, and the community at large.

258. Each Defendant created or assisted in creating the opioid epidemic, and each Defendant is jointly and severally liable for its abatement. Furthermore, each Defendant should be enjoined from continuing to create, perpetuate, or maintain said public nuisance in Newton County. Furthermore, Defendants should compensate Newton County for the funds it has expended and continues to expend for medical insurance claims for opioids that were not medically

valid, as well as increased costs of social services, health systems, law enforcement, judicial system, and treatment facilities.

VIII. SECOND CAUSE OF ACTION: COMMON LAW FRAUD AGAINST ALL DEFENDANTS

259. Newton County re-alleges and incorporates by reference each of the allegations contained in the preceding paragraphs of this Petition as though fully alleged herein.

260. At all relevant and material times, Defendants expressly and/or impliedly warranted that opioids were safe, of merchantable quality, and fit for use.

261. Defendants' superior knowledge and expertise, its relationship of trust and confidence with doctors and the public, its specific knowledge regarding the risks and dangers of opioids, and its intentional dissemination of promotional and marketing information about opioids for the purpose of maximizing sales, each gave rise to the affirmative duty to meaningfully disclose and provide all material information about the risks and harms associated with opioids.

262. At all relevant and material times, Defendants, individually and acting through their employees and agents, and in concert with each other, fraudulently represented to physicians, who Defendants knew would justifiably rely on Defendants' representations, that opioids were safe and effective for treating chronic pain.

263. Defendants' false representations were fraudulently made, with the intent or purpose that healthcare providers and patients would justifiably rely upon them, leading to the prescription, administration, filling, purchasing, and consumption of opioids in Newton County.

264. Defendants' deliberate misrepresentations and/or concealment, suppression, and omission of material facts as alleged herein include, but are not limited to:

a) Making false and misleading claims regarding the known risks of the addictive nature of opioids and suppressing, failing to disclose, and mischaracterizing the addictive nature of opioids and in concomitant costs,

such as overdoses, deaths, and heroin addiction;

b) Making false and misleading written and oral statements that opioids are more effective than traditional pain killers for chronic pain, or effective at all and/or omitting material information showing that opioids are no more effective than other non-addictive drugs for chronic pain;

c) Issuing false and misleading warnings and/or failing to issue adequate warnings concerning the risks and dangers of using opioids;

d) Making false and misleading claims downplaying the risk of addiction when using opioids and/or setting forth guidelines that would purportedly identify addictive behavior; and

e) Making false and misleading misrepresentations concerning the safety, efficacy and benefits of opioids without full and adequate disclosure of the underlying facts which rendered such statements false and misleading.

265. Defendants willfully, wantonly, and recklessly disregarded their duty to provide truthful representations regarding the safety and risk of opioids, including the fact that upon information and belief, there was suspicion for diversionary purposes.

266. Defendants made these misrepresentations with the intent that the healthcare community and patients would rely to their detriment.

267. Defendants' misrepresentations were made with the intent of defrauding and deceiving the medical community and consumers to induce and encourage the sale of opioids.

268. Defendants' fraudulent representations evidence their callous, reckless, willful, and depraved indifference to the health, safety, and welfare of consumers living in Newton County.

269. Defendants omitted, misrepresented, suppressed and concealed material facts concerning the dangers and risk of injuries associated with the use of opioids, as well as the fact that the product was unreasonably dangerous.

270. Defendants' purpose was willfully blind to, ignored, downplayed, avoided, and/or otherwise understated the serious nature of the risks associated with the use of opioids.

271. Defendants' failure to stem, rather than fuel spikes of opioid sales was intended to encourage the sale of opioids, even if the circumstances provided suspicion for diversionary purposes.

272. The treating medical community and consumers in Newton County did not know that Defendants' representations were false and/or misleading and justifiably relied on them.

273. Defendants had sole access to material facts concerning the dangers and unreasonable risks of opioids, which they intentionally concealed.

274. As a direct and proximate result of Defendants' fraudulent misrepresentations and intentional concealment of facts, upon which the medical community and consumers in Newton County reasonably relied, Newton County suffered actual and punitive damages.

IX. THIRD CAUSE OF ACTION: NEGLIGENCE AGAINST ALL DEFENDANTS

275. Newton County re-alleges and incorporates by reference each of the allegations contained in the preceding paragraphs of this Petition as though fully alleged herein.

276. Defendants have a duty to exercise reasonable care in marketing its opioids to physicians treating residents of Newton County and Newton County residents. Defendants have breached their duty by knowingly and fraudulently misrepresenting the benefits of, and downplaying the risks of, opioids for chronic pain.

277. Defendants have used deceitful marketing ploys, KOLs, Front Groups, and other schemes to increase profits at the cost of public health causing an opioid epidemic. Defendants have acted willfully, wantonly, and maliciously.

278. As a proximate result, Defendants and its agents have caused Newton County to incur excessive costs to treat the opioid epidemic in its county including, but not limited to, increased costs of social services, health systems, law enforcement, judicial system, and treatment

facilities. It was foreseeable to all Defendants that the burden of the opioid crisis would fall to counties like Newton County in the form of social and economic costs. Specifically it was foreseeable that Newton County would sustain damages as an employer obligated to provide healthcare coverage to its employees and as a local government obligated to provide public services to its citizens.

279. Newton County and its residents are therefore entitled to actual and punitive damages.

X. FOURTH CAUSE OF ACTION: GROSS NEGLIGENCE AGAINST ALL DEFENDANTS

280. Newton County re-alleges and incorporates by reference each of the allegations contained in the preceding paragraphs of this Petition as though fully alleged herein.

281. Defendants' marketing scheme to optimize profits by misrepresenting and falsely promoting opioids as the panacea to chronic pain was done intentionally.

282. Defendants' hiring of KOLs, Front Groups, and others to spread its fraudulent message that opioids were useful and beneficial for chronic pain was grossly negligent and done with conscious indifference or reckless disregard for the safety of others.

283. Each Defendant's actions and omissions as described herein, singularly or in combination with each other, were malicious resulting in damages and injuries to Newton County and its residents.

284. At every stage, Defendants knew, or should have known, that their conduct would create an unreasonable risk of physical harm to others, including Newton County and its residents, and should be held liable in punitive and exemplary damages to Newton County.

XI. FIFTH CAUSE OF ACTION: UNJUST ENRICHMENT AGAINST ALL DEFENDANTS

285. Newton County re-alleges and incorporates by reference each of the allegations contained in the preceding paragraphs of this Petition as though fully alleged herein.

286. As an expected and intended result of their conscious wrongdoing as set forth in this Petition, Defendants have profited and benefited from opioid purchases made by Newton County and its residents.

287. When Newton County and its residents purchased opioids, they expected that Defendants had provided necessary and accurate information regarding those risks. Instead, Defendants had misrepresented the material facts regarding the risks and benefits of opioids and distributed or disbursed opioids even though, upon information and belief, there was suspicion for diversionary purposes.

288. Defendants took undue advantage and received a benefit because the County bore the cost of the externalities of Defendants' wrongful conduct. Moreover, the County had no choice and was effectively required to cover these costs to Defendants' benefit.

289. Defendants have been unjustly enriched at the expense of Newton County, and Newton County is therefore entitled to damages to be determined by the jury.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully prays:

a. That the acts alleged herein be adjudged and decreed to be unlawful and that the Court enter a judgment declaring them to be so;

b. That Defendants be enjoined from, directly or indirectly through KOLs, Front Groups or other third parties, continuing to misrepresent the risks and benefits of the use of opioids for chronic pain, and from continuing to violate Texas law;

c. That Plaintiff recover all measures of damages, including punitive and exemplary damages, allowable under the law, and that judgment be entered against Defendants in favor of Plaintiff;

d. That Plaintiff recover restitution on behalf of Newton County consumers who paid for opioids for chronic pain;

e. That Plaintiff recover the costs and expenses of suit, pre- and post-judgment interest, and reasonable attorneys' fees as provided by law; and

f. That Defendants be ordered to abate the public nuisance that they created in in violation of Texas common law.

Date: December 7, 2018

Respectfully Submitted,

Newton County District Attorney

/s/Courtney Tracy Ponthier
Courtney Tracy Ponthier
Newton County District Attorney
TX State Bar No. 24060741
110 Court Street, Room 121
P.O. Drawer 36
Newton, TX 75966
Tel: (409) 379-8600
Fax: (409) 379-8603
courtney.ponthier@co.newton.tx.us

OF COUNSEL:

SIMON GREENSTONE PANATIER, P.C.

/s/Jeffrey B. Simon
Jeffrey B. Simon
TX State Bar No. 00788420
Amy M. Carter
TX State Bar No. 24004580
1201 Elm Street, Suite 3400
Dallas, Texas 75270
Tel: (214) 276-7680
Fax: (214) 276-7699
jsimon@sgptrial.com
acarter@sgptrial.com

PAUL D. HENDERSON, P.C.
Paul D. Henderson
TX State Bar No. 09426300
712 W. Division Ave.
Orange, TX 77630
Tel: (409) 883-9355
Fax: (409) 883-8377
pdhendersonlaw@aol.com

DIES & PARKHURST, L.L.P.
David Dies
TX State Bar No. 05850800
Steven L. Parkhurst
TX State Bar No. 00797206
1009 Green Avenue
Orange, TX 77630
Tel: (409) 883-0892
Fax: (409) 670-0888
ddies@dieslaw.com
sparkhurst@dieslaw.com

EXHIBIT A

Pain Physician 2012; 15:ES9-ES38 • ISSN 2150-1149

Health Policy

Opioid Epidemic in the United States

Laxmaiah Manchikanti, MD[1], Standiford Helm II, MD[2], Bert Fellows, MA[3], Jeffrey W. Janata, PhD[4], Vidyasagar Pampati, MSc[5], Jay S. Grider, DO, PhD[6], and Mark V. Boswell, MD, PhD[7]

From: [1,3,5]Pain Management Center of Paducah, Paducah, KY, and [1,2]University of Louisville, Louisville, KY; [2]Pacific Coast Pain Management Center, Laguna Hills, CA; [4]University Hospitals of Cleveland, Cleveland, OH; and [6]University of Kentucky, Lexington, KY.

Dr. Manchikanti is Medical Director of the Pain Management Center of Paducah, Paducah, KY, and Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY.
Dr. Helm is Medical Director, Pacific Coast Pain Management Center, Laguna Hills, CA.
Bert Fellows is Director Emeritus of Psychological Services at the Pain Management Center of Paducah, Paducah, KY.
Dr. Janata is Division Chief, Psychology, University Hospitals of Cleveland, Case School of Medicine, Cleveland, OH.
Vidyasagar Pampati is a Statistician at the Pain Management Center of Paducah, Paducah, KY.
Dr. Grider is Associate Professor, Department of Anesthesiology, University of Kentucky, Lexington, KY.
Dr. Boswell is Chairman, Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY

Address correspondence:
Laxmaiah Manchikanti, M.D.
2831 Lone Oak Road
Paducah, Kentucky 42003
E-mail: drlm@thepainmd.com

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: None.

Manuscript received: 03/28/2012
Accepted for publication: 04/09/2012

Free full manuscript:
www.painphysicianjournal.com

Over the past two decades, as the prevalence of chronic pain and health care costs have exploded, an opioid epidemic with adverse consequences has escalated. Efforts to increase opioid use and a campaign touting the alleged undertreatment of pain continue to be significant factors in the escalation. Many arguments in favor of opioids are based solely on traditions, expert opinion, practical experience and uncontrolled anecdotal observations. Over the past 20 years, the liberalization of laws governing the prescribing of opioids for the treatment of chronic non-cancer pain by the state medical boards has led to dramatic increases in opioid use. This has evolved into the present stage, with the introduction of new pain management standards by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) in 2000, an increased awareness of the right to pain relief, the support of various organizations supporting the use of opioids in large doses, and finally, aggressive marketing by the pharmaceutical industry. These positions are based on unsound science and blatant misinformation, and accompanied by the dangerous assumptions that opioids are highly effective and safe, and devoid of adverse events when prescribed by physicians.

Results of the 2010 National Survey on Drug Use and Health (NSDUH) showed that an estimated 22.6 million, or 8.9% of Americans, aged 12 or older, were current or past month illicit drug users, The survey showed that just behind the 7 million people who had used marijuana, 5.1 million had used pain relievers. It has also been shown that only one in 6 or 17.3% of users of non-therapeutic opioids indicated that they received the drugs through a prescription from one doctor.

The escalating use of therapeutic opioids shows hydrocodone topping all prescriptions with 136.7 million prescriptions in 2011, with all narcotic analgesics exceeding 238 million prescriptions. It has also been illustrated that opioid analgesics are now responsible for more deaths than the number of deaths from both suicide and motor vehicle crashes, or deaths from cocaine and heroin combined. A significant relationship exists between sales of opioid pain relievers and deaths. The majority of deaths (60%) occur in patients when they are given prescriptions based on prescribing guidelines by medical boards, with 20% of deaths in low dose opioid therapy of 100 mg of morphine equivalent dose or less per day and 40% in those receiving morphine of over 100 mg per day. In comparison, 40% of deaths occur in individuals abusing the drugs obtained through multiple prescriptions, doctor shopping, and drug diversion.

The purpose of this comprehensive review is to describe various aspects of crisis of opioid use in the United States. The obstacles that must be surmounted are primarily inappropriate prescribing patterns, which are largely based on a lack of knowledge, perceived safety, and inaccurate belief of undertreatment of pain.

Key words: Opioid abuse, opioid misuse, nonmedical use of psychotherapeutic drugs, nonmedical use of opioids, National Survey on Drug Use and Health, opioid guidelines.

Pain Physician 2012; 15:ES9-ES38

The Institute of Medicine (IOM) recently published a report on relieving pain in America (1,2). The report identified multiple facts, including that there are more than 116 million Americans with pain persisting from weeks to years, with financial costs ranging from $560 billion to $635 billion per year. The report alluded to the serious problem of the diversion and abuse of opioid drugs, questioning their long-term usefulness. The IOM committee reported that when opioids are used as prescribed; they can be safe and effective for acute postoperative pain, procedural pain, and patients nearing the end of life who desire more pain relief. While the IOM committee does promote pain treatment, including opioids, they do acknowledge a serious crisis in the diversion and abuse of opioids and a lack of evidence for the long-term usefulness of opioids in treating chronic pain. Along with increases in the prevalence of chronic pain, health care costs, and adverse consequences due to opioid use, the opioid crisis is escalating (1-49). Despite mounting evidence, efforts to increase opioid use based on the alleged undertreatment of pain continue (50-63). In fact, Stein (64) summarized the evidence succinctly, noting that "many arguments in favor of opioids are solely based on traditions, expert opinion, practical experience, and uncontrolled anecdotal observations."

Starting in the late 1990's, state medical boards curtailed restrictions on laws governing the prescribing of opioids for the treatment of chronic non-cancer pain, resulting in a dramatic increase in the number of prescriptions (65). This development gathered momentum with the introduction of new pain management standards for in-patient and out-patient medical care implemented by the Joint Commission on the Accreditation of Health Care Organizations (JCAHO) in 2000 (66) and an increased awareness of the right to pain relief, both of which provided justification for physicians (67-70). Other factors fueling an increase in prescriptions included aggressive marketing by the pharmaceutical industry, the promotion of opioids by numerous physicians and a call for for the increased use of opioids in the treatment of chronic non-cancer pain by myriad organizations. These positions, alongside continued assertions that pain is undertreated, were largely based on untenable science and misinformation, and contended that opioids are highly effective and safe without adverse effects when prescribed by physicians (31,60,66,71-90). Moreover, a recent examination of model guidelines for curtailing controlled substance abuse revealed that the guidelines appeared instead to condone an increase in prescribing (50,91-93). This is illustrated by the language in the model guidelines, which state (65), "no disciplinary action will be taken against a practitioner based solely on the quantity and/or frequency of opioids prescribed." Thus, the use of opioids in general, including long-acting and potent forms of opioids, have dramatically increased due to a shift in regulations largely driven by published, albeit extremely weak, evidence suggesting that opioids are not only highly effective, but also safe in selected persons with chronic non-cancer pain, even though this selection criteria are extremely weak and these guidelines have only facilitated overuse of opioids (31,71,94-98). Nearly 2 decades later, the scientific evidence for the effectiveness of opioids for chronic non-cancer pain remains unclear (35,71,96,99-119). In addition to ongoing concerns with regard to the lack of effectiveness of opioids in chronic non-cancer pain (31-38,96,99-119), there is growing evidence of multiple physiologic and non-physiologic adverse effects, such as opioid hyperalgesia (32,95,96,107,112-124), misuse and abuse (31-39,71,95,96,102,103,110-115,125-140), the inability of providers to identify and monitor misuse and overuse (31,32,36,95,96,126,127,130,138-151), and a steady increase in opioid-related fatalities (32,34,37,129,130,152-163). In fact, in 2008 drug poisoning in the United States has been reported to contribute to one death every 15 minutes (160). Furthermore, opioids have been shown to contribute to one death every 36 minutes in the United States in 2008. Correlating with these fatalities, sales and substance abuse treatment admissions have increased substantially (125-127,159,160,164-168).

With the above background highlighting a steady increase in fatalities with opioid use and very little evidence of effectiveness, it remains to be seen who will ultimately bear the responsibility for the premature adoption of opioids as a treatment standard (116). It has been speculated that in the coming years, there will likely be an extensive "postmortem" on the massive opioid treatment movement and the escalating social crisis that has accompanied it (116). It is universally accepted that this massive treatment movement has led to huge collateral damage in terms of diversion, misuse, and abuse of opioids. The widespread use of opioids for chronic non-cancer pain is in direct violation of the established cardinal principles of medical intervention – that there be compelling evidence of the benefit of a therapy prior to its large-scale use (116).

A cautious approach has been advocated in recent years by many (17,33,35,49,110-115,117-119,169). This

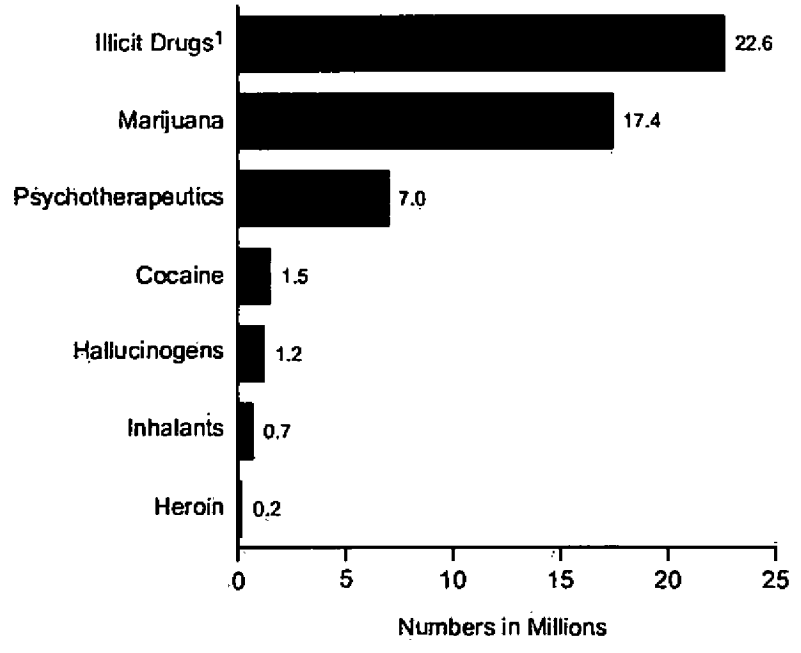
manuscript is undertaken to evaluate the escalating opioid crisis which although heavily regulated, continues to be uncontrolled.

1.0 Non-Medical Use of Psychotherapeutic Drugs

1.1 Current Non-Medical Use

Results of the 2010 National Survey on Drug Use and Health (NSDUH) (170), an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), showed that an estimated 22.6 million, or 8.9% of Americans, age 12 or older, were current (past month) illicit drug users. Illicit drugs include marijuana, cocaine, heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics (defined in this survey as prescription-type pain relievers, tranquilizers, stimulants, and sedatives) used non-medically. Marijuana was the most commonly used illicit drug with 17.4 million current (past month) users, or 6.9% of the US population. Cocaine was used by 1.5 million, whereas hallucinogens were used in the past month by 1.2 million persons (Fig. 1 and Table 1). Next to marijuana, 7.0 million (27%) persons age 12 or older had used prescription-type psychotherapeutic drugs non-medically in the past month (current use). Of these, 5.1 million had used pain relievers. The category of psychotherapeutics used in the tables and figures includes the nonmedical use of any prescription-type pain relievers, tranquilizers, stimulants, or sedatives. However, over-the-counter substances are not included in these studies. The categories of nonmedical use of psychotherapeutics and pain relievers were well ahead of the illicit use of cocaine, hallucinogens, inhalants, methamphetamine, heroin, and lysergic acid diethylamide (LSD).

Overall, there has been an increase in the current use of all illicit drugs and marijuana, without any change for psychotherapeutics and hallucinogens and a decrease for cocaine from 2002 to 2010, as shown in Fig. 2.



[1]Illicit Drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically.

Fig. 1. *Past month illicit drug use among persons aged 12 or older: 2010.*

Source: Substance Abuse and Mental Health Services Administration. *Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings.* http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012.

Table 1. *Types of illicit drug use in the past month among persons aged 12 or older: Numbers in thousands, from 1998 to 2010.*

Drugs	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	12-Year % change from 1998 to 2010
Nonmedical Use of Psychotherapeutics[2,3]	2,477 (1.1%)	3,952 (1.8%)	3,849 (1.7%)	4,811 (2.1%)	6,287 (2.7%)	6,451 (2.7%)	6,110 (2.5%)	6,491 (2.7%)	7,095[b] (2.9%[b])	6,895[a] (2.8%[a])	6,224 (2.5%)	6,953 (2.8%)	6,967 (2.7%)	181%
Pain Relievers	--	2,621 (1.2%)	2,782 (1.2%)	3,497 (1.6%)	4,377 (1.9%)	4,693 (2.0%)	4,404 (1.8%)	4,658 (1.9%)	5,220 (2.1%)	5,174 (2.1%)	4,747 (1.9%)	5,257 (2.1%)	5,100 (2.0%)	NA
OxyContin[a]	--	--	--	--	--	--	325 (0.1%)	334 (0.1%)	276 (0.1%[a])	369 (0.1%)	435 (0.2%)	510 (0.2%)	564 (0.2%)	NA
Tranquilizers	655 (0.3%)	1,097 (0.5%)	1,000 (0.4%)	1,358 (0.6%)	1,804 (0.8%)	1,830 (0.8%)	1,616 (0.7%)	1,817 (0.7%)	1,766 (0.7%)	1,835 (0.7%)	1,800 (0.7%)	2,010 (0.8%)	2,160 (0.9%)	230%
Stimulants	633 (0.3%)	950 (0.4%)	788 (0.4%)	1,018 (0.5%)	1,303[b] (0.6%[b])	1,310[b] (0.6%[b])	1,312[b] (0.5%[b])	1,188[b] (0.5%[b])	1,385[b] (0.6%[b])	1,053 (0.4%)	904 (0.4%)	1,290 (0.5%)	1,077 (0.4%)	70%
Sedatives[3]	210 (0.1%)	229 (0.1%)	175 (0.1%)	306 (0.1%)	436[b] (0.2%[b])	294 (0.1%)	265 (0.1%)	272 (0.1%)	385 (0.2%[a])	346 (0.1%)	234 (0.1%)	370 (0.1%)	374 (0.1%)	78%
Marijuana and Hashish	11,016 (5.0%)	10,458 (4.7%)	10,714 (4.8)	12,122 (5.4%)	14,584 (6.2%)	14,638 (6.2%)	14,576 (6.1%)	14,626 (6.0%)	14,813 (6.0%)	14,448 (5.8%)	15,203 (6.1%)	16,718 (6.6%)	17,373 (6.9%)	58%
Cocaine	1,750 (0.8%)	1,552 (0.7%)	1,213 (0.5%)	1,667 (0.7%)	2,020 (0.9%)	2,281 (1.0%)	2,021 (0.8%)	2,397 (1.0%)	2,421 (1.0%)	2,075	1,855	1,637 (0.7%)	1,466 (0.6%)	-16%
TOTAL ILLICIT DRUGS[1]	13,615 (6.2%)	13,829 (6.3%)	14,027 (6.3%)	15,910 (7.1%)	19,522 (8.3%)	19,470 (8.2%)	19,071 (7.9%)	19,720 (8.1%)	20,357 (8.3%)	19,857 (8.0%)	20,077 (8.0%)	21,813 (8.7%)	22,622 (8.9%)	66%

-- Not available.

Note: 2002 to 2008 data is based on 2008 National Survey on Drug Use and Health Survey Report.

a Difference between estimate and 2008 estimate is statistically significant at the 0.05 level.b Difference between estimate and 2008 estimate is statistically significant at the 0.01 level.

1 Illicit Drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. Illicit Drugs Other

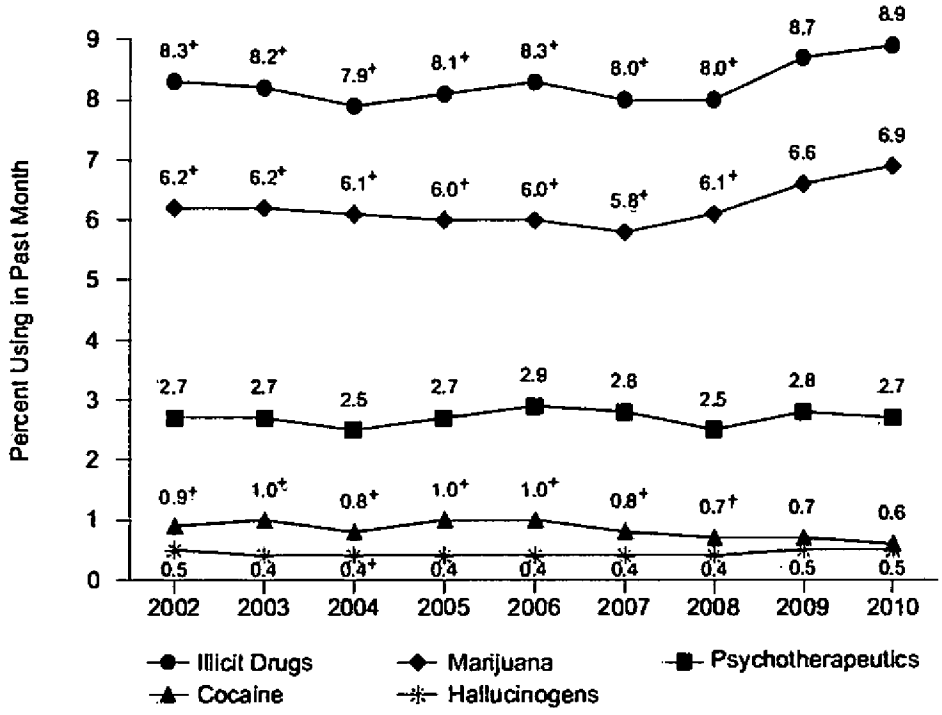
Than Marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. The estimates for Nonmedical Use of Psychotherapeutics, Stimulants, and Methamphetamine incorporated in these summary estimates do not include data from the methamphetamine items added in 2005 and 2006.

2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives and does not include over-the counter drugs.

3 Estimates of Nonmedical Use of Psychotherapeutics, Stimulants, and Methamphetamine in the designated rows include data from methamphetamine items added in 2005 and 2006 and are not comparable with estimates presented in NSDUH reports prior to the 2007 National Findings report. For the 2002 through 2005 survey years, a Bernoulli stochastic imputation procedure was used to generate adjusted estimates comparable with estimates for survey years 2006 and later.

Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 1998 - 2010.

www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012



+ Difference between this estimate and the 2010 estimate is statistically significant at the .05 level.

Fig. 2. *Past month use of selected illicit drugs among persons aged 12 or older: 2002-2010.*
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

1.2 Past Year Initiates

In 2010, there were 2.4 million persons age 12 or older who used psychotherapeutics non-medically for the first time within the past year. Numbers of new users for specific psychotherapeutics in 2010 were 2.0 million for pain relievers, 1.2 million for tranquilizers, 624,000 for stimulants, and 252,000 for sedatives (Table 2 and Fig. 3). The specific drug categories with the largest number of recent initiatives among persons age 12 or older were nonmedical use of pain relievers (2,004 million) and marijuana (2,426 million), followed by nonmedical use of tranquilizers (1,238 million), ecstasy (0.937 million), inhalants (0.793 million), cocaine (0.637 million), and stimulants (0.624 million) (Fig. 3). More strikingly, in 2010, the number of new nonmedical users of OxyContin (oxycodone) age 12 or older was 598,000 with an average age at first use of 22.8 years among those age 12 to 49 (170).

1.3 Past Year Use

The analysis of long-term statistics based on yearly use of illicit drugs is disturbing. The past year use of illicit drugs in 2010 was 38.806 million, or 15.3% of the population (Table 3). Nonmedical use of psychotherapeutics for the past year in the 2010 survey was 16.031 million or 6.3% population age 12 or older, compared to 2.6% of the population in 1998. Of importance is the fact that nonmedical use of psychotherapeutics was just behind marijuana and hashish with use by 11.5% of the population age 12 or older in 2010, increased from 8.6% in 1998. Overall, nonmedical use of psychotherapeutics increased 178% from 1998 to 2010, compared to marijuana 56% and cocaine at 17%.

1.4 Lifetime Use

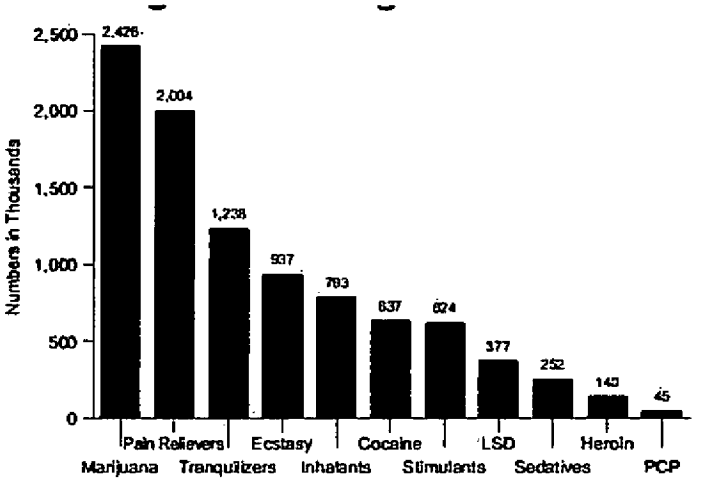
Lifetime use of illicit drugs (lifetime use indicates use of a specific drug at least once in the respondent's

Table 2. *Past year initiates for illicit drugs from 1998 to 2010 (numbers in thousands) for 12 years.*

Drugs	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	12-Year % change from 1998 to 2010
Pain Relievers[2]	1,548	1,810	2,268	2,400	2,320	2,456	2,422	2,193	2,150	2,147	2,176	2,179	2,004	29%
Tranquilizers	860	916	1,298	1,212	1,184	1,071	1,180	1,286	1,112	1,232	1,127	1,226	1,238	44%
Stimulants[2]	648	706	808	853	783	715	793[a]	647	845[b]	642	599	702	624	-4%
Sedatives	147	164	191	225	209	194	240	247	267	198	181	186	252	71%
Marijuana	2,498	2,640	2,746	2,793	2,196	1,973	2,142	2,114	2,063	2,090	2,208	2,361	2,426	-3%
Cocaine	868	917	1,002	1,140	1,032[b]	986[b]	998[b]	872[a]	977[b]	906[b]	722	617	637	-27%
Heroin	140	121	114	154	117	92	118	108	91	106	114	180	140	0%

Note: 2002 to 2008 data is based on 2008 National Survey on Drug Use and Health Survey Report.
-- Not available.
a Difference between estimate and 2008 estimate is statistically significant at the 0.05 level.
b Difference between estimate and 2008 estimate is statistically significant at the 0.01 level.
1 Illicit Drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. Illicit Drugs Other Than Marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. The estimates for Nonmedical Use of Psychotherapeutics, Stimulants, and Methamphetamine incorporated in these summary estimates do not include data from the methamphetamine items added in 2005 and 2006. See Section B.4.8 in Appendix B of the Results from the 2008 National Survey on Drug Use and Health: National Findings.
2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives and does not include over-the counter
drugs.
3 Estimates of Nonmedical Use of Psychotherapeutics, Stimulants, and Methamphetamine in the designated rows include data from methamphetamine items added in 2005 and 2006 and are not comparable with estimates presented in NSDUH reports prior to the 2007 National Findings report. For the 2002 through 2005 survey years, a Bernoulli stochastic imputation procedure was used to generate adjusted estimates comparable with estimates for survey years 2006 and later.
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

lifetime), including psychotherapeutics, among persons age 12 or older has been increasing over the years (Table 4). In 2010, the lifetime use of illicit drugs among persons age 12 or older was slightly more than 2009 with 119,508 or 47.1% of the population. Similarly, nonmedical use of psychotherapeutics remained the same from 2009 with 20.4% in 2010, or almost 51.6 million using prescription psychotherapeutic drugs for nonmedical purposes. Among the subgroups, only OxyContin increased significantly from 1.9 million in 2005 to 6.1 million in 2010, or 0.8% of the population in 2005 to 2.4% in 2010 (171). Lifetime use of illicit drugs in per-



Note: The specific drug refers to the one that was used for the first time, regardless of whether it was the first drug used or not.

Fig. 3. *Past year initiates for specific illicit drugs among persons aged 12 or older: 2010.*
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

sons age 12 or older was topped by marijuana (41.9% of the population) followed by nonmedical use of psychotherapeutics (20.4% of the population).

1.5 Abuse Based on Age

In 2010, young adults age 18 to 25 demonstrated rates of current use of illicit drugs to be higher (21.5%) than for youths age 12 to 17 (10.1%) and adults age 26 or older (6.6%), with 6.9% using marijuana, 2.7% using psychotherapeutics non-medically, 0.6% using cocaine, and 0.5% using hallucinogens among young adults 18-25 (Fig. 4). Past month nonmedical use of prescription-type drugs among young adults increased from 20.2% in 2002 to 21.5% in 2010. This was primarily due to an increase in the rate of pain reliever use which was 4.1% in 2002 and 4.9% in 2006 (170). As illustrated in Figure 5, overall illicit drug use increased from 8.3% to 8.9% in 2010 in the age group from 18 to 25.

Rates of past month illicit drug use varied with age. Through the adolescent years from 12 to 17, the rates of current illicit drug use in 2010 increased from 4.0% at ages 12 or 13, to 9.3% at ages 14 or 15, to 16.6% at ages 16 or 17 (170). The highest rate of 23.1% was noted among persons age 18 to 20, with the next highest rate among 21 to 25 year olds 20.5% (Fig. 6) (144). In 2010, adults age 26 or older were less likely to be current drug users than youths age 12 to 17 or young adults age 18 to 25 (6.6 versus 10.1 and 21.5%, respectively). However, there were more drug users age 26 or older (12.8 million) than users in the 12-to-17-year age group (2.5 million) and 18-to-25-year age group (7.3 million) combined.

1.6 Abuse Based on Gender

In 2010, the survey results were similar to prior years with males being more likely than females to be current illicit drug users (11.2% versus 6.8%). Males were more likely than females to be past month users of marijuana (9.1% versus 4.7%). Rates of past month nonmedical use of psychotherapeutic drugs among males and females was 3% and 2.5%, pain relievers was 2.3% and 1.7%, cocaine was 0.8% and 0.4% and hallucinogens was 0.6% and 0.3% (170).

1.7 Abuse During Pregnancy

Among pregnant woman age 15 to 44 years, a significantly lower proportion of women used illicit drugs in the past month (4.4%) compared to 10.9% of their

Table 3. *Types of illicit drug use in the past year among persons aged 12 or older: numbers in thousands from 1998 to 2010 (12 years).*

Drugs	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	12-year % change from 1998 to 2010
Nonmedical Use of Psychotherapeutics[2,3]	5,759 (2.6%)	9,220 (4.2%)	8,761 (3.9%)	11,102 (4.9%)	14,795 (6.3%)	15,163 (6.4%)	14,849 (6.2%)	15,346 (6.3%)	16,482 [b] (6.7% [b])	16,280[a] (6.6%[a])	15,166 (6.1%)	16,006 (6.4%)	16,031 (6.3%)	178%
Pain Relievers	--	6,582 (3.0%)	6,466 (2.9%)	8,353 (3.7%)	10,992[a] (4.7%)	11,671 (4.9%)	11,256 (4.7%)	11,815 (4.9%)	12,649 (5.1% [a])	12,466 (5.0%)	11,885 (4.8%)	12,405 (4.9%)	12,213 (4.8%)	85% From 1999
OxyContin*	--	--	--	--	--	--	1,213[a] (0.5%)	1,226 (0.5%)	1,323 (0.5%)	1,422 (0.6%)	1,459 (0.6%)	1,677 (0.7%)	1,869 (0.7%)	54% From 2004
Tranquilizers	1,940 (0.9%)	2,728 (1.2%)	2,731 (1.2%)	3,673 (1.6%)	4,849 (2.1%)	5,051 (2.1%)	5,068 (2.1%)	5,249 (2.2%)	5,058 (2.1%)	5,282 (2.1%)	5,103 (2.0%)	5,460 (2.2%)	5,581 (2.2%)	188%
Stimulants3	1,489 (0.7%)	2,291 (1.0%)	2,112 (0.9%)	2,486 (1.1%)	3,380[b] (1.4%[b])	3,031[a] (1.3%[b])	3,254[b] (1.4%[b])	3,088[a] (1.3%[b])	3,791[b] (1.5%[b])	2,998 (1.2%)	2,639 (1.1%)	3,060 (1.2%)	2,887 (1.1%)	94%
Sedatives	522 (0.2%)	631 (0.3%)	611 (0.3%)	806 (0.4%)	981[b] (0.4%[b])	831 a (0.3%[a])	737 (0.3%)	750 (0.3%)	926 b (0.4%[b])	864 [a] (0.3%[a])	621 (0.2%)	811 (0.3%)	907 (0.4%)	56%
Marijuana and Hashish	18,710 (8.6%)	19,102 (8.6%)	18,589 (8.3%)	21,086 (9.3%c)	25,755 (11.0%[a])	25,231 (10.6%)	25,451 (10.6%)	25,375 (10.4%)	25,378 (10.3%)	25,085 (10.1%)	25,768 (10.3%)	28,521 (11.3%)	29,206 (11.5%)	56%
Cocaine	3,811 (1.7%)	3,742 (1.7%)	3,328 (1.5%)	4,186 (1.9%c)	5,902[a] (2.5%[b])	5,908[a] (2.5%[b])	5,658 (2.4% a)	5,523 (2.3%)	6,069[b] (2.5%[b])	5,738 (2.3%)	5,255 (2.1%)	4,797 (1.9%)	4,449 (1.8%)	17%
TOTAL ILLICIT DRUGS1	23,115 (10.6%)	25,402 (11.5%)	24,535 (11.0%)	28,409 (12.6%[c])	35,132 (14.9%[a])	34,993 (14.7%)	34,807 (14.5%)	35,041 (14.4%)	35,775 (14.5%)	35,692 (14.4%)	35,525 (14.2%)	37,957 (15.1%)	38,806 (15.3%)	68%

-- Not available.

Note: 2002 to 2010 data is based on 2010 National Survey on Drug Use and Health Survey Report. a Difference between estimate and 2010 estimate is statistically significant at the 0.05 level. b Difference between estimate and 2010 estimate is statistically significant at the 0.01 level.

1 Illicit Drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used nonmedically. Illicit drugs other than marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used non-medically. The estimates for nonmedical use of psychotherapeutics, stimulants, and methamphetamine incorporated in these summary estimates do not include data from the methamphetamine items added in 2005 and 2006.

2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives and does not include over-the counter drugs.

3 Estimates of nonmedical use of psychotherapeutics, stimulants, and methamphetamine in the designated rows include data from methamphetamine items added in 2005 and 2006 and are not comparable with estimates presented in NSDUH reports prior to the 2007 National Findings report. For the 2002 through 2005 survey years, a Bernoulli stochastic imputation procedure was used to generate adjusted estimates comparable with estimates for survey years 2006 and later.

Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170). Access date 2/22/2012

Table 4. *Types of illicit drugs of lifetime use among persons aged 12 or older: numbers in thousands, 1998 – 2010.*

Drug	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	12-Year % change from 1998 to 2010
Nonmedical Use of Psychotherapeutics[2]	20,193 (9.2%)	34,076 (15.4%)	32,443 (14.5%)	36,028 (16.0%)	47,958 [b] (20.4%)	49,001[b] (20.6%)	49,157 (20.4%)	49,571 a (20.4%)	50,965 (20.7%)	50,415 (20.3%)	51,970 (20.8%)	51,771 (20.6%)	51,641 (20.4%)	156%
Pain Relievers	--	19,888 (9.0%)	19,210 (8.6%)	22,133 (9.8%)	29,611 [b] (12.6% [b])	31,207 [b] (13.1% [a])	31,768 [b] (13.2% [a])	32,692 [b] (13.4%)	33,472 (13.6%)	33,060 [a] (13.3%)	34,861 (14.0%)	35,046 (13.9%)	34,776 (13.7%)	75% From 1999
OxyContin®	--	--	--	--	1,924 [b] (0.8% [b])	2,832 [b] (1.2% [b])	3,072 [b] (1.3% [b])	3,481 [b] (1.4% [b])	4,098 [b] (1.7% [b])	4,354 (1.8%)	4,842 (1.9%)	5,829 (2.3%)	6,121 (2.4%)	218% From 2002
Tranquilizers	7,726 (3.5%)	13,860 (6.3%)	13,007 (5.8%)	13,945 (6.2%)	19,267 [b] (8.2%)	20,220 (8.5%)	19,852 [a] (8.3%)	21,041 (8.7%)	21,303 (8.7%)	20,208 (8.2%)	21,476 (8.6%)	21,755 8.6%)	22,103 (8.7%)	186%
Stimulants	9,614 (4.4%)	15,922 (7.2%)	14,661 (6.6%)	16,007 (7.1%)	23,496 [b] (10.0% [b])	23,004 [a] (9.7% [b])	22,297 (9.3% b)	20,983 (8.6%)	22,468 (9.1% [a])	21,654 (8.7%)	21,206 (8.5%)	21,930 (8.7%)	21,660 (8.5%)	125%
Sedatives	4,640 (2.1%)	7,747 (3.5%)	7,142 (3.2%)	7,477 (3.3%)	9,960 [a] (4.2% [b])	9,510 (4.0% [a])	9,891 (4.1% a)	8,982 (3.7%)	8,822 (3.6%)	8,396 (3.4%)	8,882 (3.6%)	8,605 (3.4%a)	7,631 (3.2%)	64%
Marijuana and Hashish	72,070 (33.0%)	76,428 (34.6%)	76,321 (34.2%)	83,272 (36.9%[c])	94,946 [b] (40.4%)	96,611 [b] (40.6%)	96,772 b (40.2%)	97,545 [b] (40.1%)	97,825 [b] (39.8% [a])	100,518 (40.6%)	102,404 (41.0%)	104,446 (41.5%)	106,232 (41.9%)	47%
Cocaine	23,089 (10.6%)	25,406 (11.5%)	24,896 (11.2%)	27,788 (12.3%)	33,910 [b] (14.4%)	34,891 [a] (14.7%)	34,153 b (14.2%)	33,673 [b] (13.8%)	35,298 (14.3%)	35,882 (14.5%)	36,773 (14.7%)	36,599 (14.5%)	37,210 (14.7%)	61%
TOTAL ILLICIT DRUGS1	78,123 (35.8%)	87,734 (39.7%)	86,931 (38.9%)	94,140 (41.7%[c])	108,255 b (46.0%)	110,205 [b] (46.4%)	110,057 b (45.8% a)	112,085 [b] (46.1%)	111,774 [b] (45.4% [b])	114,275[a] (46.1%)	117,325 (47.0%)	118,705 (47.1%)	119,508 (47.1%)	53%

-- Not available.

Note: 2002 to 2010 data is based on 2010 National Survey on Drug Use and Health Survey Report.

a Difference between estimate and 2010 estimate is statistically significant at the 0.05 level.

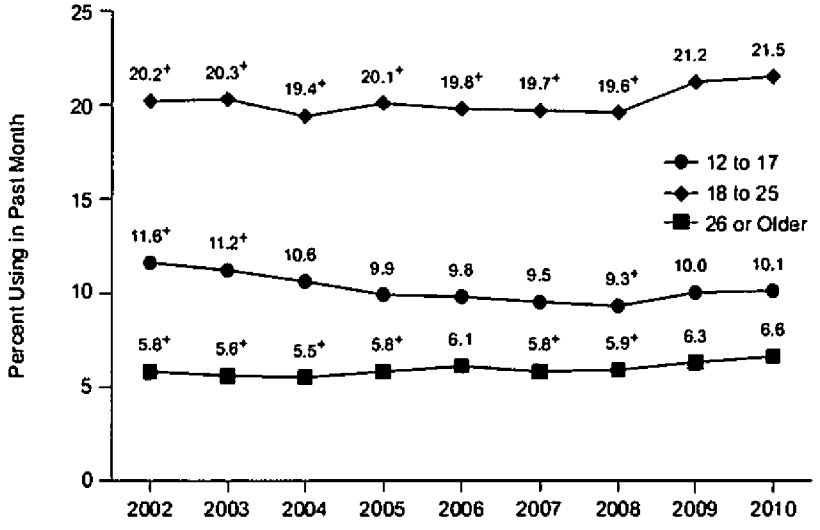
b Difference between estimate and 2010 estimate is statistically significant at the 0.01 level.

1 Illicit Drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used non-medically. Illicit drugs other than marijuana include cocaine (including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used non-medically. The estimates for nonmedical use of psychotherapeutics, stimulants, and methamphetamine incorporated in these summary estimates do not include data from the methamphetamine items added in 2005 and 2006.

2 Nonmedical use of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives and does not include over-the counter drugs.

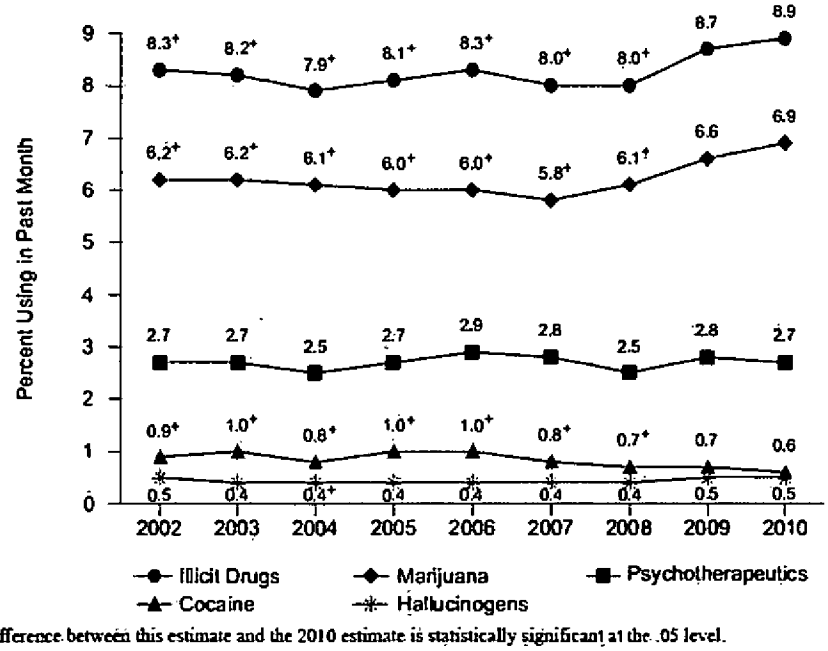
3 Estimates of nonmedical use of psychotherapeutics, stimulants, and methamphetamine in the designated rows include data from methamphetamine items added in 2005 and 2006 and are not comparable with estimates presented in NSDUH reports prior to the 2007 National Findings report. For the 2002 through 2005 survey years, a Bernoulli stochastic imputation procedure was used to generate adjusted estimates comparable with estimates for survey years 2006 and later.

Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012



+ Difference between this estimate and the 2010 estimate is statistically significant at the .05 level.

Fig. 4. *Comparative analysis of past month use of illicit drugs among various age groups.*
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012



+ Difference between this estimate and the 2010 estimate is statistically significant at the .05 level.

Fig. 5. *Past month use of selected illicit drugs among young adults aged 18 to 25: 2002-2010.*
Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

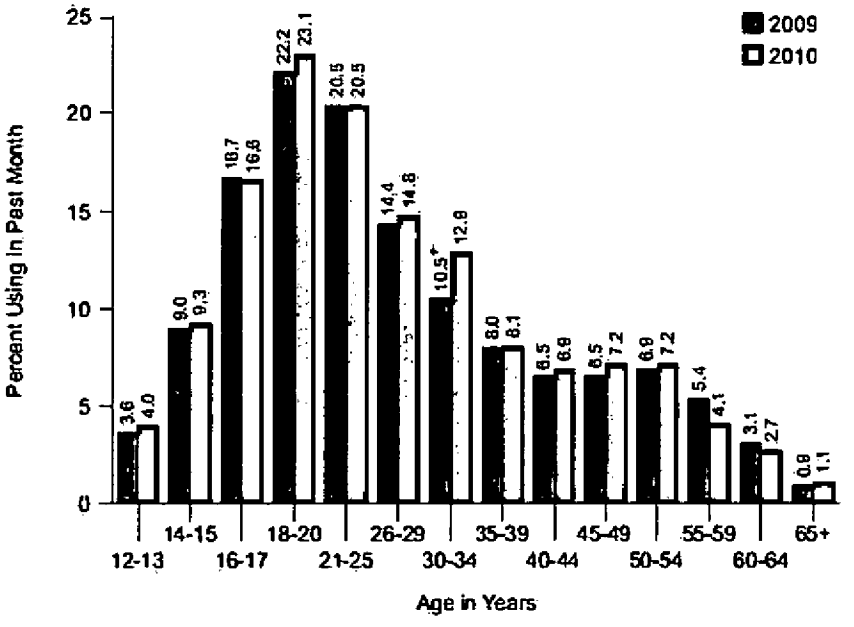


Fig. 6. *Past month illicit drug use among persons aged 12 or older, by age: 2009 and 2010.*
Source: Substance Abuse and Mental Health Services Administration, Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf (170) Access date 2/22/2012

nonpregnant counterparts. These figures are based on data averaged for 2009 and 2010 (170).

1.8 Abuse Based on Employment

Employment also seemed to have a significant influence in 2010. Among adults age 18 or older, the rate of illicit drug use was higher for unemployed persons (17.5%) than for those who were employed full time (8.4%) or part time (11.2%) (170).

1.9 Regional Variations

There were also differences based on geographic area among persons age 12 or older in 2010. The rate of current illicit drug use in 2010 was 11.0% in the West, 9.4% in the Northeast, 8.2% in the Midwest, and 7.8% in the South (170). Further, the rate of current illicit drug use in metropolitan areas was higher than the rate in non-metropolitan areas with 9.4% in large metropolitan counties, 8.8% in small metropolitan counties, and 7.5% in non-metropolitan counties as a group (170).

1.10 Drug Abuse Among Criminals

In 2010, an estimated 1.5 million adults age 18 or older who were on parole or supervised release from jail during the past year had higher rates of dependence on or abuse of a substance (27%) than their counterparts who were not on parole or supervised release during the past year (8.7%). In 2010, probation status was associated with substance dependence or abuse. The rate of substance dependence or abuse was 29.9% among adults who were on probation during the past year, which was significantly higher than the rate among adults who were not on probation during the past year was 8.3% (170).

1.11 Driving Under the Influence

Driving under the influence of illicit drugs is a criminal act and dangerous to the public. In 2010, 10.6 million persons, or 4.2% of the population age 12 or older, reported driving under the influence of illicit drugs during the past year. This rate was highest among young adults age 18 to 25 with 12.7% (170).

1.12 Frequency of Abuse

Among past year marijuana users age 12 or older in 2010, the following patterns were revealed (170):

- 15.7% used marijuana on 300 or more days within the past 12 months, translating to 4.6 million using marijuana on a daily or almost daily basis over a 12-month period.
- 39.9%, or 6.9 million, used the drug on 20 or more days in the past month (current use).

2.0 Mental Health Problems and Nonmedical Use Of Drugs

The NSDUH survey of 2010 evaluated the prevalence and treatment of serious mental illness (SMI), serious psychological distress (SPD), and major depressive episode (MDE) and the association of these problems with substance use and substance dependency or abuse. SPD is an overall indicator of the past 30 days of psychological distress, whereas MDE is defined as a period of at least 2 weeks when a person experienced a depressed mood or loss of interest or pleasure in daily activities and had symptoms that met the criteria for a major depressive disorder (171). Further, SPD indicates a respondent recently experienced heightened distress symptomatology that may be affecting health and behavior during the past 30 days. However, this distress may be part of a chronic psychological disturbance (even SMI) or may represent a temporary disturbance that could subside after a brief period of adjustment.

2.1 Serious Medical Illness and Drug Abuse

The prevalence of SMI in 2010 was shown in 11.4 million adults, representing 5.0% of all adults, with the highest rates being in adults age 18 to 25 (7.7%) and lowest for adults age 50 or older (3.2%) as shown in Figure 7 (171). The prevalence of SPD among women age 18 or older was higher (6.5%) than among men (3.4%) in that age group (171).

2.2 Major Depressive Episodes and Drug Abuse

The prevalence of a MDE in 2010 was 6.8% of persons age 18 or older, or 15.5 million adults, with at least one MDE in the past year. The number of adults who had past year MDE was 6.8%. Even then, the past year

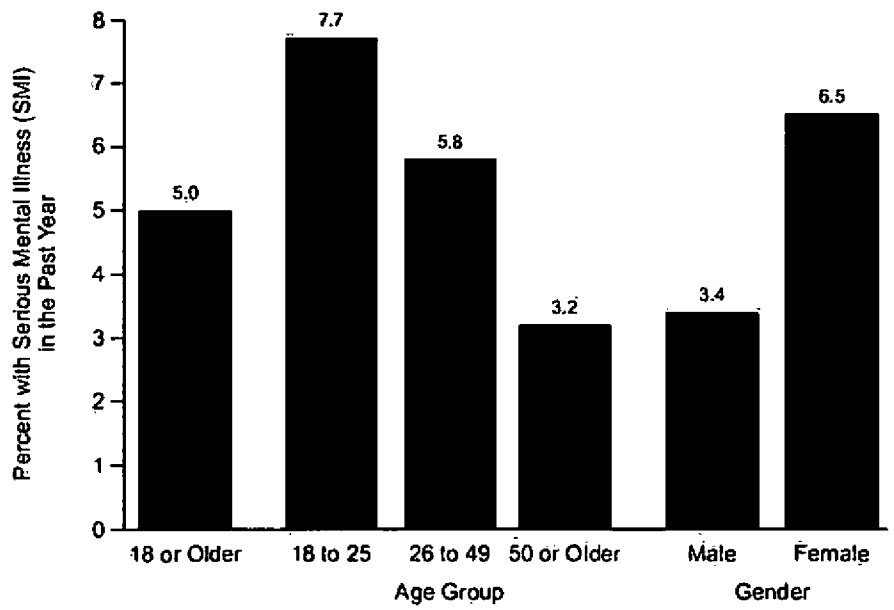


Fig. 7. *Serious mental illness, psychological distress, and nontherapeutic drug use, among persons age 18 and older, by age, 2010.* Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Mental Health Findings. www.samhsa.gov/data/NSDUH/2k10MH_Findings/2k10MHResults.pdf (171) Access date 2/23/2012

prevalence of MDE in 2010 was lower for those age 50 or older (5.6%) compared with rates among persons age 18 to 25 (8.2%) and those age 26 to 49 (7.5%). However, the past year prevalence of MDE was higher among adult females than among adult males, 8.4% versus 5.1%. In addition, among women, past year MDE rates were higher with 11.3% for 18 to 25 year olds, 9.2 for 26 to 49 year olds compared with those of 50 or older with only 6.7%. Further, the prevalence of MDE also varied by race and ethnicity with the highest rate among persons reporting 2 or more races (10.8%), while rates for single race groups were 7.3% among whites, 5.6% among Hispanics, 7.7% among American Indians or Alaska Natives, 5.8% among blacks, and 3.8% among Asians.

In addition, in 2010 the past prevalence of MDE with severe impairment for adults age 18 or older was higher among unemployed persons (9.3%) than among persons employed full time (5.4%).

In 2010, an adult age 18 or older with a combination of a MDE and substance use and dependence or abuse in the past year was more likely than those with MDE to have used an illicit drug in the past year (22.0% versus 7.9%) (171). A similar pattern was observed for specific types of past year illicit drug use, such as marijuana and the nonmedical use of prescription-type psychotherapeutics. Figure 8 illustrates substance abuse in adults by MDE.

The prevalence of a MDE in youths age 12 to 17 in 2010 showed that 1.9 million (8.9%) reported at least one MDE during the past year. Among youths age 12 to 17, the past year prevalence of MDE ranged from 3.3% among 12-year-olds to 10.9% among those age 16, and 10.3% among those age 17 (171).

Among youths with MDE age 12 to 17, 37.2% had used illicit drugs in 2010, in contrast to 37.4% in 2008. This was higher than the 17.8% of youths in the past year that did not have a MDE but had used illicit drugs. This pattern, however, was similar to specific types of illicit drug use including marijuana and the nonmedical use of prescription-type psychotherapeutics (171).

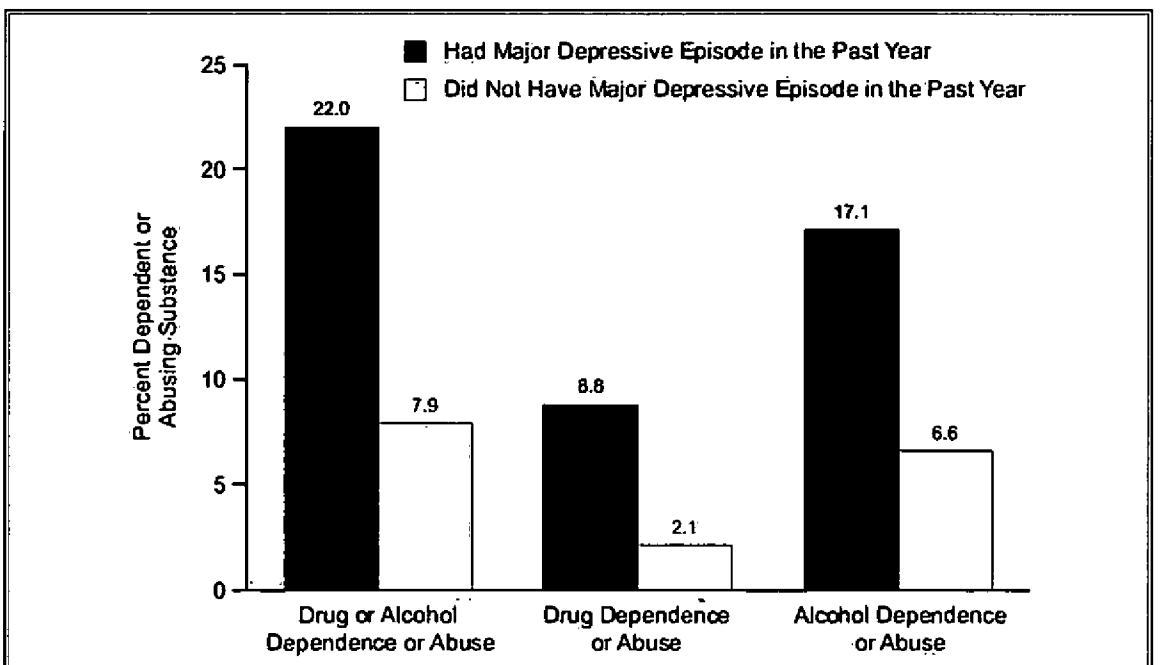


Fig. 8. *Substance dependence or abuse among adults age 18 or older, by major depressive episode in the past years, 2010.* Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Mental Health Findings. www.samhsa.gov/data/NSDUH/2k10MH_Findings/2k10MHResults.pdf (171) Access date 2/23/2012

3.0 Where Do Non-Therapeutic Drugs Come From?

Among persons aged 12 or older in 2009-2010 who used pain relievers nonmedically in the past 12 months, 55% obtained pain relievers from a friend or relative for free (170). Among the remaining 45%, 11.4% bought them from a friend or relative (which was significantly higher than the 8.9% from 2007-2008), and 4.8% essentially stole them from a friend or relative (Fig. 9). However, only one in 6 or 17.3% indicated that they received the drugs through a prescription from one doctor, while only 4.4% received pain relievers from a drug dealer or other stranger, and 0.4% bought them on the Internet, with no significant changes from 2007 to 2008.

Even more striking is the fact that in 2009-2010, 41.5% of past year methamphetamine users reported that they obtained the methamphetamine they used most recently for free from a friend or relative, with an additional 30.7% buying it from a friend or relative (170).

4.0 Escalating Use Of Therapeutic Opioids

The escalating use of therapeutic opioids, specifically in high doses over long periods of time, or even lifetime use of long-acting drugs, and the combination of long and short-acting drugs continue to have serious consequences for costs of health care and economic stability.

The data overwhelmingly suggest that the increased supply of opioids, high medical users, doctor shoppers, and patients with multiple comorbid factors contribute to the majority of fatalities. The quadrupled sales of opioid analgesics between 1999 and 2010 are a perfect example of the therapeutic opioid explosion. The data on sales and distribution of opioids show an increase from 96 mg morphine equivalents per person in the United States in 1997 to 710 mg per person in 2010 (34,153). This has been estimated to be the equivalent of 7.1 kg of opioid medication per 10,000 persons or enough to supply every adult American with 5 mg of hydrocodone every 6 hours for 45 days. Sales of hy-

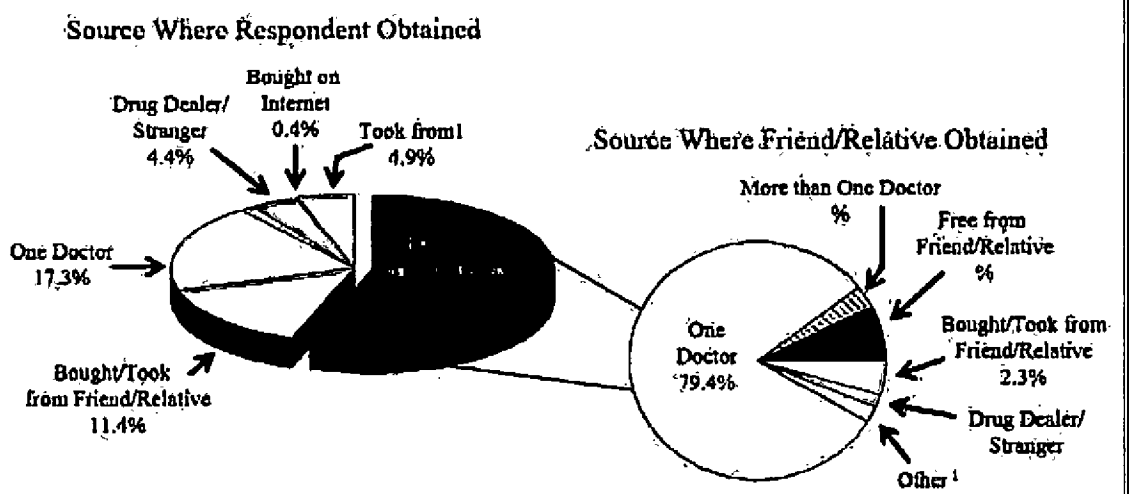


Fig. 9. *Source where pain relievers were obtained for most recent nonmedical use among past year users age 12 or older: 2009-2010.* Source: Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Mental Health Findings. www.samhsa.gov/data/NSDUH/2k10MH_Findings/2k10MHResults.pdf (171) Access date 2/23/2012

drocodone have increased by 280% from 1997 to 2007, whereas methadone usage has increased 1,293% and oxycodone usage by 866%, as illustrated in Table 5 (32). The estimated number of prescriptions filled for opioids exceeded 256 million in the United States in 2009, with 234 million prescriptions for immediate-release (IR) opioids and 22.9 million for extended-release (ER) opioids with significant increases from 21.3 million for

Table 5. *Retail sales of opioid medications (grams of medication) from 1997 to 2007.*

Drug	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	% of Change from 1997
Methadone	518,737	692,675 (34%)	964,982 (39%)	1,428,840* (48%)	1,892,691 (32%)	2,649,559 (40%)	3,683,881 (39%)	4,730,157 (28%)	5,362,815 (13%)	6,621,687 (23%)	7,228,219 (9%)	1293%
Oxycodone	4,449,562	6,579,719 (48%)	9,717,600 (48%)	15,305,913 (58%)	19,927,286 (30%)	22,376,892 (12%)	26,655,152 (19%)	29,177,530 (9%)	30,628,973 (5%)	37,034,220 (21%)	42,977,043 (16%)	866%
Fentanyl Base	74,086	90,618 (22%)	107,141 (18%)	146,612* (37%)	186,083 (27%)	242,027 (30%)	317,200 (31%)	370,739 (17%)	387,928 (5%)	428,668 (11%)	463,340 (8%)	525%
Hydromorphone	241,078	260,009 (8%)	292,506 (12%)	346,574* (18%)	400,642 (16%)	473,362 (18%)	579,372 (22%)	655,395 (13%)	781,287 (19%)	901,663 (15%	1,011,028 (12%)	319%
Hydrocodone	8,669,311	10,389,503 (20%)	12,101,621 (16%)	14,118,637 (17%)	15,594,692 (10%)	18,822,619 (21%)	22,342,174 (19%)	24,081,900 (8%)	25,803,543 (7%)	29,856,368 (16%)	32,969,527 (10%)	280%
Morphine	5,922,872	6,408,322 (8%)	6,804,935 (6%)	7,807,511 (15%)	8,810,700 (13%)	10,264,264 (16%)	12,303,956 (20%)	14,319,243 (16%)	15,054,846 (5%)	17,507,148 (16%)	19,051,426 (9%)	222%
Codeine	25,071,410	26,018,054 (4%)	23,917,088 (-8%)	23,474,865* (-2%)	23,032,641 (-2%)	22,633,733 (-2%)	21,865,409 (-3%)	20,264,555 (-7%)	18,960,038 (-6%)	18,762,919 (-1%)	18,840,329 (0.4%)	-25%
Meperidine (Pethidine)	5,765,954	5,834,294 (1%)	5,539,592 (-5%)	5,494,898* (-1%)	5,450,204 (-1%)	5,412,389 (-1%)	5,239,932 (-3%)	4,856,644 (-7%)	4,272,520 (-12%)	4,160,033 (-3%)	3,936,179 (-5%)	-32%
Total	50,713,010	56,273,194 (11%)	59,445,465 (6%)	35,962,089.84 (15%)	75,294,939 (11%)	82,874,845 (10%)	92,987,076 (12%)	98,456,163 (6%)	101,251,950 (6%)	115,272,706 (14%)	126,477,091 (10%)	149%

Number in parenthesis is percentage of change from previous year.
* For year 2000 data is not available, the average of 1999 and 2001 was taken.
Source: www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html Access date: 8/25/2010
Source for 2007 data - www.justice.gov/ndic/pubs33/33775/dlinks.htm
Adapted from: Manchikanti L, et al. Therapeutic use, abuse, and nonmedical use of opioids: A ten-year perspective. Pain Physician 2010; 13:401-435 (32).

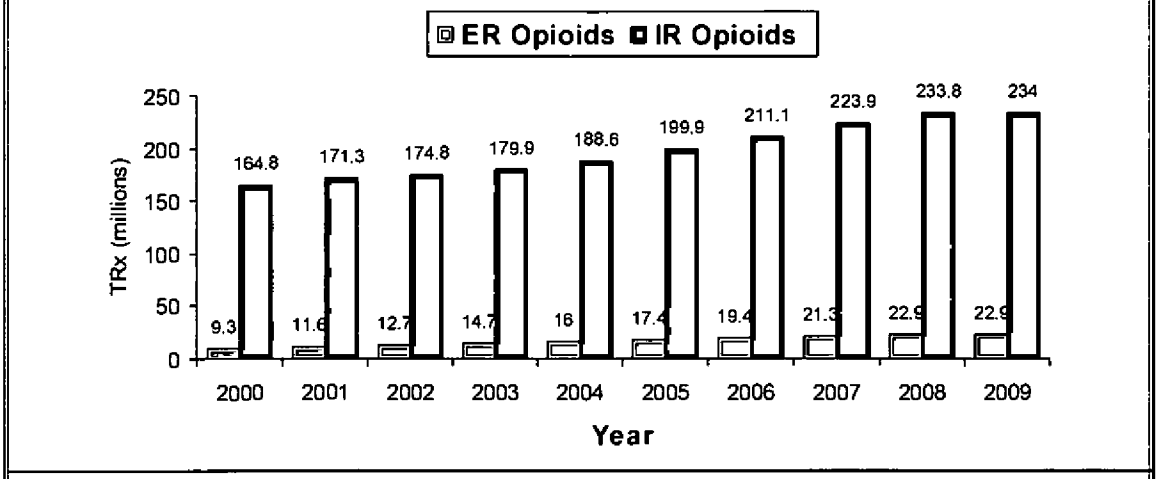


Fig. 10. *Total number of prescriptions dispensed for ER/LA and IR opioids from U. S. outpatient retail pharmacies, year 2000 – 2009 (173).*
Source: SDI, Vector One ®: National (174).

ER opioids and from 223.9 million for IR opioids from 2007 as illustrated in Figure 10 (172-174). The data are even more compelling when compared from 2002 to 2009 with an increase from 9.3 million for ER opioids to 22.9 million, a 146% increase, and from 164.8 million to 234 million for IR opioids, a 42% increase with an annual increase of 21% for ER opioids and 6% for IR opioids. Most prescriptions were for hydrocodone and oxycodone-containing products (84.9%) and issued for short treatment courses, 19.1% for less than 2 weeks, 65.4% for 2-3 weeks. Of these, however, approximately 12% of the prescriptions were issued to those aged 10 to 29 years. This may signal a potential problem for this population, as this is also the population most likely to abuse drugs and develop addictions (172). In addition, the data also illustrates an 8-fold increase in stimulant prescriptions from 1991 to 2009 as illustrated in Fig. 11.

Table 6 illustrates hydrocodone with acetaminophen being the number one prescription from 2006 through 2011 (175). However, narcotic analgesics constitute number 4 in the proportion of patients treated in selected therapies with hypertension, topping at 42.4 million and narcotic analgesics at 15.6 million, constituting number 10 in spending in leading therapy areas with oncologicals constituting 23.2 billion and narcotic analgesics constituting 8.3 billion in 2011 as illustrated in Tables 7 and 8 and Fig. 12 (175).

The United Nations Office on Drugs and Crime, in an evaluation of the world supply of opioid, shows 90% of the global consumption of morphine, fentanyl, and oxycodone registered in 2009 occurring in Australia, Canada, New Zealand, the United States and several European countries (60,85).

Another World Health Organization (WHO) report (87) showed that based on the statistics from the International Narcotics Control Board (INCB) in 2003, 6 developed countries accounted for 79% of global morphine consumption, whereas developing countries which represent 80% of the world population accounted for only about 6% of global morphine consumption. In addition, the most recent data showed that in 2007, 6 developed countries reported the highest level of morphine consumption and 132 of the 160 signatory countries that require reporting of consumption were below the global mean as illustrated in Fig. 13. This simply illustrates that millions of patients with moderate to severe pain caused by different diseases and conditions may not be getting treatment to alleviate their suffering in some countries, while more of them are receiving it in other countries such as the United States, which uses 99% of the world's supply of hydrocodone and 83% of the world's oxycodone (176-178).

Gram for gram, people in the United States consume more narcotic medication than any other nation worldwide. The International Narcotic Control Board, a division of the United States, estimates global pharmaceutical companies produce more than 75 tons a year of oxycodone, compared with 11.5 tons in 1999.

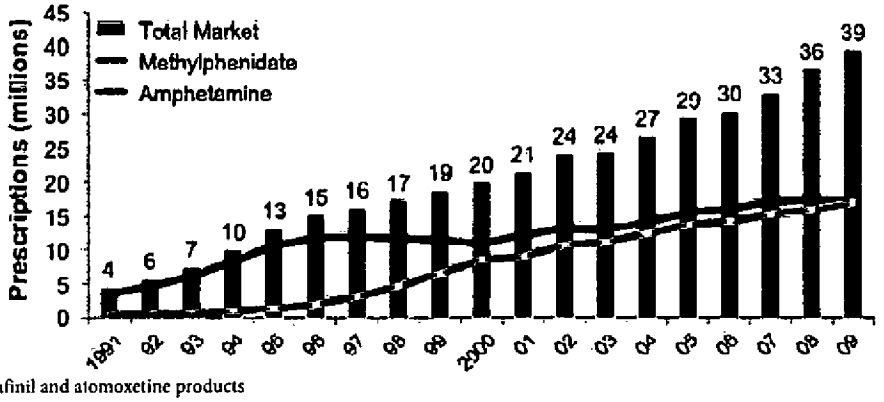


Fig. 11. Projected number of prescriptions for stimulants dispensed by U.S. retail pharmacies, 1991-2009.*
Source: SDI, Vector One*: National (174).

Table 6. *Top medicines by prescriptions.*

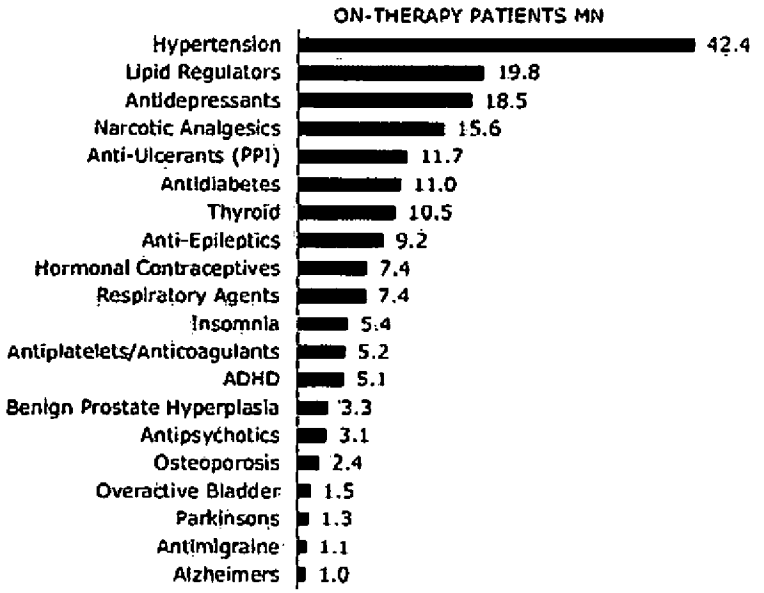
DISPENSED PRESCRIPTIONS MN		2007	2008	2009	2010	2011
Total US Market		3,825	3,866	3,949	3,993	4,024
1	Hydrocodone/acetaminophen	120.9	125.5	129.4	132.1	136.7
2	Levothyroxine sodium	97.4	98.9	100.2	103.2	104.7
3	Simvastatin	49.0	68.0	84.1	94.4	96.8
4	Lisinopril	71.5	77.2	83.0	87.6	88.8
5	Amlodipine besylate	40.8	46.0	52.1	57.8	62.5
6	Omeprazole (RX)	27.7	35.8	45.6	53.5	59.4
7	Metformin HCL	49.2	51.6	53.8	57.0	59.1
8	Azithromycin	47.1	51.9	54.7	53.6	56.2
9	Amoxicillin	54.0	51.3	52.9	52.4	53.8
10	Alprazolam	41.4	43.3	45.3	47.7	49.1
11	Hydrochlorothiazide	48.5	48.5	47.9	47.8	48.1
12	Zolpidem tartrate	34.5	39.1	42.7	43.7	44.6
13	Atorvastatin	65.8	58.5	51.7	45.3	43.3
14	Furosemide	44.7	44.4	43.8	43.6	42.3
15	Oxycodone/acetaminophen	31.3	33.6	36.7	37.9	38.8
16	Fluticasone	23.9	26.2	30.1	34.8	38.4
17	Citalopram HBR	18.1	22.6	27.3	32.2	37.8
18	Metoprolol tartrate	43.5	38.4	41.1	38.9	37.8
19	Sertraline HCL	33.4	33.7	34.8	36.2	37.6
20	Metoprolol succinate	33.0	41.5	26.9	33.0	34.5
21	Warfarin sodium	34.4	34.9	35.7	35.6	33.9
22	Tramadol HCL	20.6	23.3	25.5	28.0	33.9
23	Potassium	36.7	35.8	35.2	34.7	33.7
24	Prednisone	25.9	27.1	27.8	28.7	33.7
25	Atenolol	45.0	42.0	39.5	36.4	33.4

Source: IMS Health, National Prescription Audit, Dec. 2011 (175).
Notes: Report reflects prescription-bound products including insulins and excluding other products such as OTC. Table shows leading active-ingredients or ingredient fixed-combinations, and includes those produced by both branded and generic manufacturers. Includes all prescriptions dispensed through retail pharmacies - including independent and chain drug stores, food store pharmacies and mail order as well as long-term care facilities. Prescription counts are not adjusted for length of therapy. 90-day and 30-day prescriptions are both counted as one prescription.

Updated February 17, 2012.

of which more than 80% of is consumed in the United States. The International Narcotics Board also reports that U.S. demand for hydrocodone, the most commonly prescribed opioid, is about 27.4 million grams annually compared to 3,237 grams for Britain, France, Germany, and Italy combined (61,177,178).

Caudill-Slosberg et al (165) in one of the earliest evaluations demonstrated that opioid use doubled from 8% in 1980 to 16% in 2000. The data also illustrates that from 1999 to 2002, 4.2% of U.S. adults reported the use of opioid analgesics for pain within the past month (179). In a report of opioid use in one of the states in the United States (Utah) (180), the data showed that 20.8% of adults had been prescribed an opioid in the last year and that 29.1% of these prescriptions were for long-term pain. Sullivan et al (181) also showed over a 6 year period that the proportion of enrollees receiving opioids with a diagnosis of chronic



Source: IMS Health, LifeLink, Dec 2011

Fig. 12. *Treated patients in selected therapy.*

Table 7. *Spending based on the therapeutic class.*

SPENDING $BN		2007	2008	2009	2010	2011
Total US Market		280.5	285.7	300.7	308.6	319.9
1	Oncologics	18.1	19.7	21.5	22.3	23.2
2	Respiratory Agents	15.1	16.0	18.1	19.3	21.0
3	Lipid Regulators	19.4	18.1	18.6	18.8	20.1
4	Antidiabetics	12.2	13.6	15.8	17.7	19.6
5	Antipsychotics	12.8	14.3	14.7	16.2	18.2
6	Autoimmune Diseases	7.6	8.6	9.7	10.6	12.0
7	Antidepressant	11.7	11.7	11.5	11.6	11.0
8	HIV Antivirals	6.2	7.1	8.2	9.3	10.3
9	Anti-Ulcerants	14.6	14.2	14.1	11.9	10.1
10	Narcolic Analgesics	6.7	7.3	8.0	8.4	8.3
11	ADHD	4.0	4.7	5.8	6.7	7.9

SPENDING $BN		2007	2008	2009	2010	2011
12	Platelet Aggregation Inhibitors	5.0	5.7	6.5	7.1	7.8
13	Angiotensin II Inhibitors	6.5	7.6	8.6	8.7	7.6
14	Multiple Sclerosis	3.4	4.1	5.0	5.8	7.1
15	Vaccines (Pure, Comb, Other)	5.9	5.0	4.7	5.7	6.3
16	Anti-Epileptics	10.0	11.1	6.9	5.6	5.9
17	Erythropoietins	4.1	4.5	4.7	4.8	5.2
18	Immunostimulating Agents	8.4	6.9	6.3	6.1	5.1
19	Hormonal Contraceptives	4.1	4.1	4.1	4.2	4.5
20	Antivirals, excl. Anti-HIV	3.6	3.9	4.8	3.2	3.7

Source: IMS Health, National Prescription Audit, Dec. 2011 (175).

Notes:
Therapy areas are based on proprietary IMS Health definitions. Report reflects prescription-bound products including insulins and excluding other products such as OTC. Includes all prescriptions dispensed through retail pharmacies - including independent and chain drug stores, food store pharmacies and mail order as well as long-term care facilities. Prescription counts are not adjusted for length of therapy. 90-day and 30-day prescriptions are both counted as one prescription.

Updated February 17, 2012.

Table 8. *Top therapeutic classes by prescriptions.*

DISPENSED PRESCRIPTIONS MN		2007	2008	2009	2010	2011
Total US Market		3,825	3,866	3,949	3,993	4,024
1	Antidepressants	237	241	247	254	264
2	Lipid Regulators	233	242	254	260	260
3	Narcotic Analgesics	231	239	241	244	238
4	Antidiabetics	165	166	169	172	173
5	Ace Inhibitors (Plain & Combo)	159	163	166	168	164
6	Beta Blockers (Plain & Combo)	162	164	163	162	161
7	Respiratory Agents	147	147	152	153	153
8	Anti-Ulcerants	134	139	146	147	150
9	Diuretics	137	135	132	131	128
10	Anti-Epileptics	102	110	116	122	128
11	Tranquillizers	98	101	104	108	111
12	Thyroid Preparations	103	104	105	107	110
13	Calcium Antagonists (Plain & Combo)	87	90	93	96	98
14	Antirheumatic Non-Steroid	90	91	92	93	97
15	Hormonal Contraceptives	94	94	93	91	90
16	Angiotensin II Inhibitors	83	86	85	84	86
17	Broad Spectrum Penicillins	77	74	77	76	77
18	Macrolides & Similar Type Antibiotics	63	66	69	67	69
19	Hypnotics & Sedatives	58	60	63	63	63
20	Vitamins & Minerals	60	59	58	58	60

Source: IMS Health, National Prescription Audit, Dec. 2011 (175).
Appendix notes:
Therapy areas are based on proprietary IMS Health definitions. Report reflects prescription-bound products including insulins and excluding other products such as OTC. Includes all prescriptions dispensed through retail pharmacies - including independent and chain drug stores, food store pharmacies and mail order as well as long-term care facilities. Prescription counts are not adjusted for length of therapy. 90-day and 30-day prescriptions are both counted as one prescription.

Updated February 17, 2012.

non-cancer pain and opioid prescriptions increase. Opioids are also used commonly in combination with sedative hypnotics. Vogt et al (182) in an evaluation of analgesic usage for low back pain and its impact on health care costs and service use showed that in 2001, a total of $1.4 million was spent on opioids, which constituted 68% of prescriptions for analgesics.

The data from reports and pain management settings is disconcerting. Over 90% of patients received opioids for chronic pain management (32,169,172,183-188). Even more alarming, however, is the fact that the majority of the prescriptions are from outside pain management settings. Volkow et al (172) showed that only a small proportion of prescriptions were from pain clinics or specialists from anesthesiology in 2009. Moreover, Deyo et al (31) illustrated that approximately 20% of patients in primary care settings were long-time opioid users with 61% receiving a course of opioids. In young veterans, Wu et al (189) showed that prevalence of chronic opioid use increased from 3% in 2003 to 4.5% in 2007. Patients on average were exposed to 2 different opioids and had 3 different opioid prescribers. Not surprisingly, 80% of the opioid prescriptions during the study were prescribed by pri-

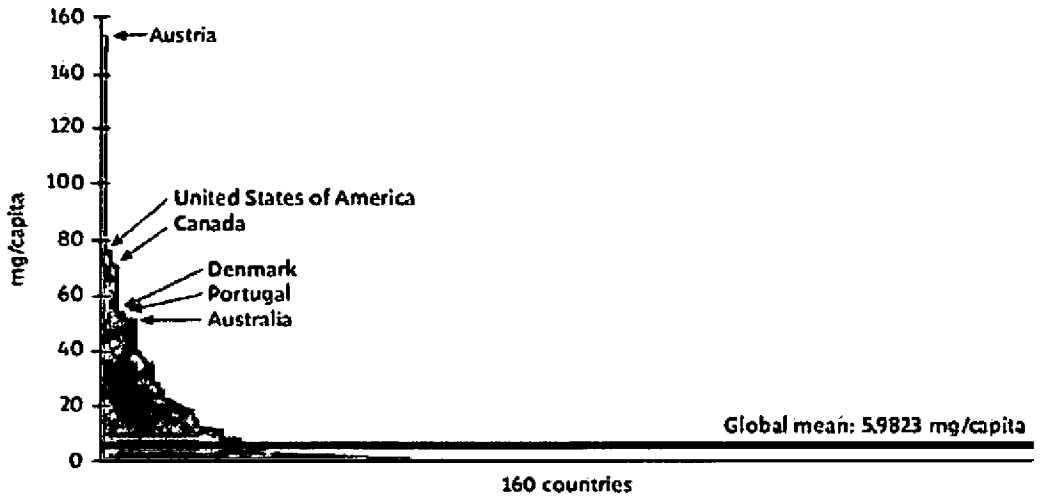


Fig. 13. *Global morphine consumption in 2007 (mg/capita).*
Source: International Narcotics Control Board, United Nations data. Graphic created by the Pain and Policy Study Group, University of Wisconsin/WHO Collaborating Center, 2009.

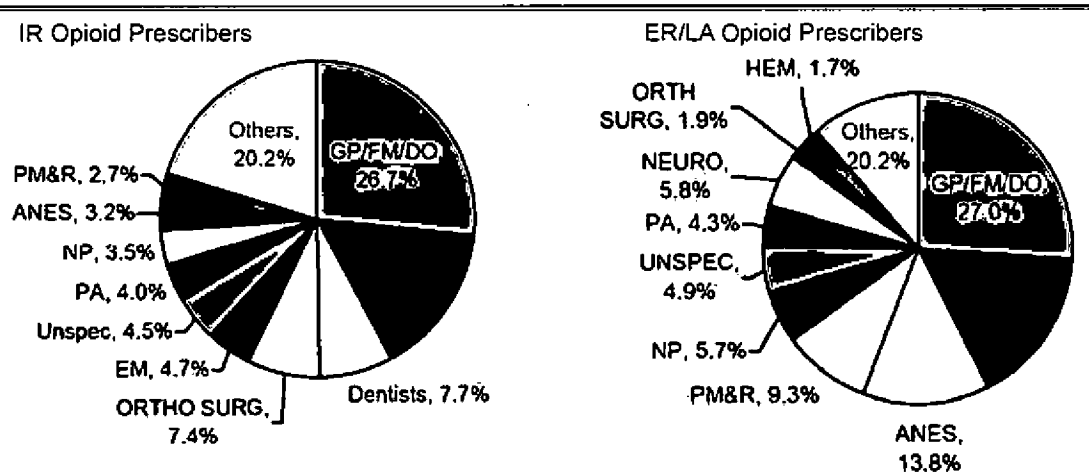


Fig. 14. *Total number of prescriptions dispensed in the U.S. by top 10 prescribing specialties for IR and ER/LA opioids, year 2009 (173).* Source: SDI, Vector One ®: National (174).

mary care providers, and less than 1% was from pain specialists.

In fact, the data illustrates that in 2009 (Fig. 14), among the top 10 specialties of those prescribing immediate release opioids were general practitioners/family medicine 26.7%, internal medicine 15.4%, anesthesiologists constituting 3.2%, and physical medicine and rehabilitation specialists constituting 2.7% (173,174). In contrast, for ER or long-acting opioids in 2009, anesthesiologists constituted 13.8% and physical medicine and rehabilitation constituted 9.3%, with general practitioners, family medical doctors, osteopaths, and internal medicine specialists still dominating the field with 27% and 16.8%, in essence exceeding their prescriptions of immediate release opioids (173,174).

5.0 Relationship of Escalating Opioid Use and Adverse Consequences

While numerous adverse effects have been reported, ever increasing opioid related fatalities, including drug poisoning deaths, are crucial. In the United States, in 2008, one or more prescription drugs were involved in 20,044 of the 27,153 deaths with a specified drug. Opioid pain relievers were involved in 14,800 drug overdose deaths, compared to 11,500 of 27,500 fatal unintended drug overdose deaths in 2007 – an increase of 3,300 in just one year (160). Alarmingly, in 2007 there were more opioid analgesic overdose deaths than overdoses involving heroin and cocaine combined (Fig. 15). In addition, during the same time frame, drug-related suicides also increased, with opioid analgesics being involved in roughly 3,000 of the 8,400 overdose deaths in the United States in 2007 that were suicide or of undetermined intent (190). Complicating these grave statistics, for every unintentional overdose death related to an opioid analgesic, 9 are admitted for substance abuse treatment, 35 visit emergency departments, 161 report drug abuse or dependence, and 461 report non-medical uses of opioid analgesics (34). Not surprisingly, in 2007, non-suicidal drug poisoning deaths exceeded both motor vehicle traffic and suicide deaths in 20 states, with data from Ohio illustrating that the number of deaths from unintentional drug poisoning surpassed the numbers of deaths from both suicide and motor vehicle crashes combined (190-192). Thus, it has been concluded that opioid analgesics contributed to fatalities based on opioid abuse and increasing doses, doctor shopping, and other aspects of drug abuse as illustrated in Fig. 16 (160). The data from emergency department visits sadly illustrate that opioids, sedatives, and non-prescription sleep aides are often taken more than prescribed or solely for the feeling they cause, and that this trend is steadily increasing (170).

The Centers for Disease Control and Prevention (CDC) (34) also reported the percentage of prescription drug overdoses by risk group in the United States. This report showed that approximately 80% of prescribed low-doses (less than 100 mg of morphine equivalent dose per day – considered as high dose by many) were by a single practitioner, accounting for an estimated 20% of all prescription overdoses (Fig. 17). In contrast, among the remaining 20% of patients, 10% of prescribed high doses (greater than 100 mg morphine equivalent dose per day) (193-195) per day of opioids by single prescribers account for an estimated 40% of the prescription opioid overdoses (131,195). The remaining 10% of patients seeing multiple doctors and typically involved in drug diversion contribute to 40% of overdoses (152). Furthermore, among persons who died of opioid overdoses, a significant proportion did not have a prescription in their records for the opioid that killed them; in West Virginia, Utah, and Ohio, 25% to 66% of those who died of pharmaceutical overdose used opioids originally prescribed to someone

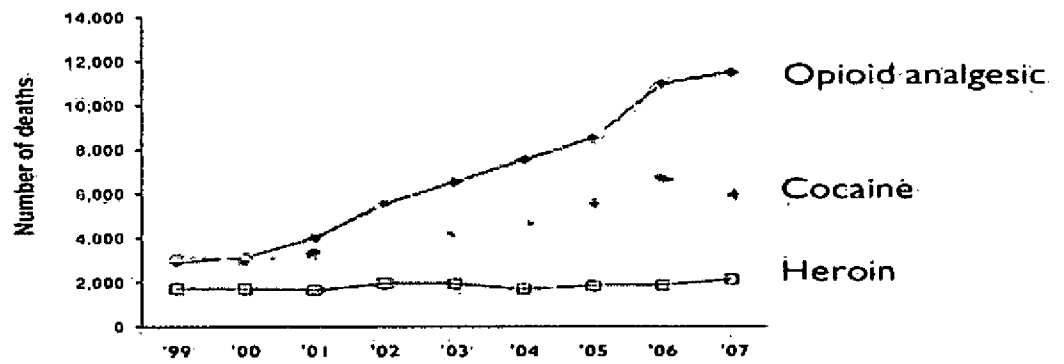
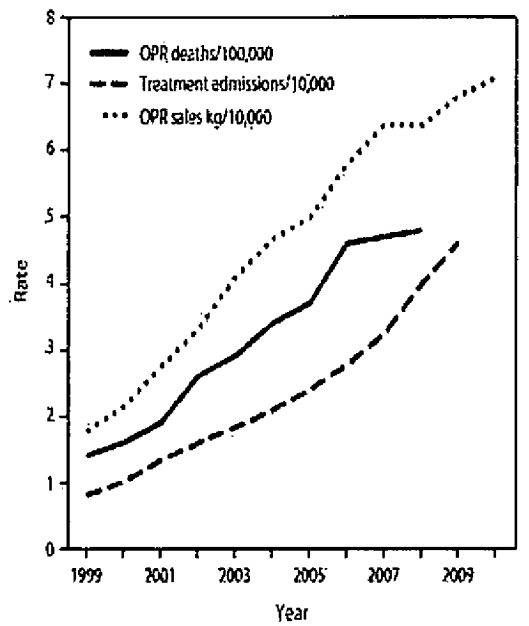


Fig. 15. *Deaths from unintentional drug overdoses in the United States according to major type of drug, 1999-2007.*
Source: Centers for Disease Control and Prevention. Unintentional Drug Poisoning in the United States. July 2010. http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf (190).



* Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold.

Fig. 16. *Rates of opioid pain reliever overdose death, opioid pain relief treatment admissions, and kilograms of opioid pain relievers sold – United States, 1999-2010.*
Source: Centers for Disease Control and Prevention. Vital signs: Overdoses of prescription opioid pain relievers – United States, 1999-2008. MMWR. Morb. Mortal Wkly. Rep. 60, 1487-1492 (2011) (160).

else (152,192,196).

The responsible opioid prescription community considers that the adverse consequences of appropriately prescribed and used opioids are least considered, as the blame is placed predominantly on abuses and overuses (49,71,116-119). Consequently, it is coupled with a lack of evidence regarding long-term benefits and ample evidence that the increased prescription of opioids is fueling an epidemic of addiction and overdose deaths. This crisis is rooted in a lack of education and misinformation, leading to overprescribing and a tendency to focus on ineffective strategies (49,71,197-199). In fact, the majority of cases involving injury and death occur in people using opioids exactly as prescribed, not just those misusing or abusing them (71). Even more importantly, most studies indicate that patients on long-term opioid therapy are unlikely to stop even if analgesia and function are poor and safety issues arise. Frequently, despite good relief and improvement in function with modalities other than opioids including interventional techniques and surgery, patients continue on opioids (200-215).

Even though there is no evidence to support the previous teaching that long-acting opioids can provide better analgesia, and less risk for abuse than immediate release products (32,71,96,100,103,107,116-119,216), the use of higher doses, with a combination of short-acting and long-acting opioids, continues to escalate. Thus, it is believed that commencing long-acting opioid therapy is often the starting point for high dose opi-

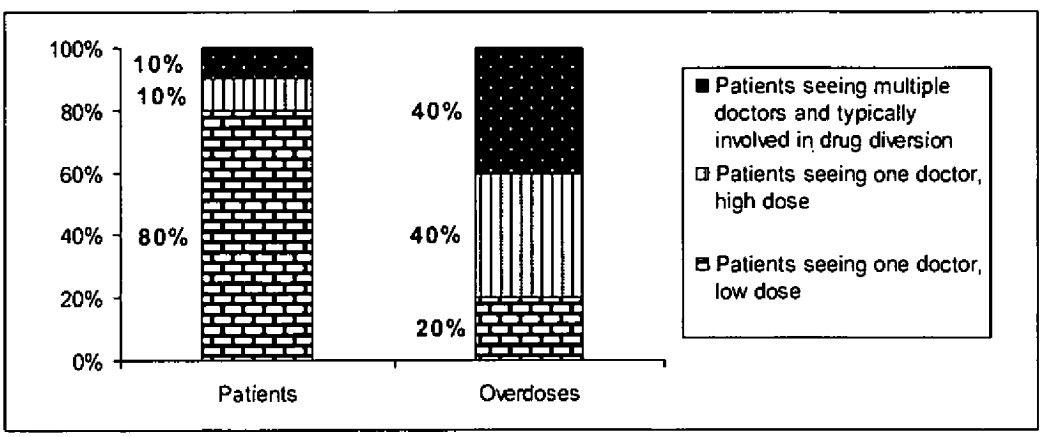


Fig. 17. *Percentage of patients and prescription drug overdoses, by risk group – United States.*
Source: Centers for Disease Control and Prevention. CDC grand rounds: Prescription drug overdoses – a U.S. epidemic. MMWR. Morb. Mortal Wkly. Rep. 61, 10-13 (2012) (34).

oid therapy, a practice that growing evidence suggests is harmful to patients and increases the black market availability of opioids through diversion (71,217-222).

Multiple studies in the literature (23,32,37,46-49,223-236) have reported an association between opioid prescribing and overall health status, with increased disability, medical costs, subsequent surgery, and continued or late opioid use. Overall, the epidemiologic studies are less positive with regards to improvement in function and quality of life with opioids in chronic pain patients (110,116-119,170,232,237). In fact, in an epidemiologic study from Denmark (23) where opioids are prescribed liberally for chronic pain, it was demonstrated that in patients receiving opioids, pain was worse, health care utilization was higher, and activity levels were lower compared to a matched cohort of chronic pain patients not using opioids. This study suggested that when opioids are prescribed liberally, even if some patients benefit, the overall population does not. Another study (33) also reported worse pain, higher health care utilization, and lower activity levels in opioid-treated patients compared to matched cohort of chronic pain patients not using opioids. Sjøgren et al (49) in a population-based cohort study on chronic pain and the role of opioids, showed that the odds of recovery from chronic pain were almost 4 times higher among individuals not using opioids compared with individuals using opioids. In addition, they also showed that use of strong opioids was associated with poor health-related quality of life, and higher risk of death. In addition, opioid abuse in chronic pain has been highly prevalent, along with illicit drug usage in addition to misuse or abuse of therapeutic opioids (32,143-152,183-188).

Conclusion

What emerges from the available data utilized in this review is the conclusion that over the past 20 years there has been an escalation of the therapeutic use of opioids and other psychotherapeutics as well as their abuse and nonmedical use. As a consequence of the fact that hydrocodone has become the number one prescribed medication in America, it is not difficult to see the significant impact that this has had on the overall patterns of abuse and nonmedical use, particularly since the illicit use of prescribed psychotherapeutics (including opioids, which are currently at the top of that list) now overshadows the use of nonprescription illicit drugs. Drug dealers are no longer the primary source of illicit drugs. Our greatest enemy is now inappropriate prescribing patterns, based on a lack of knowledge, perceived safety, and undertreatment of pain.

Acknowledgments

The authors wish to thank Sekar Edem for assistance in the search of the literature, Tom Prigge, MA, and Alvaro Gómez, MA, for manuscript review, and Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript. We would like to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript

References

1. Institute of Medicine (IOM). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. The National Academies Press, Washington, DC, June 29, 2011.
2. Pizzo PA, Clark NM. Alleviating suffering 101 – Pain relief in the United States. *N Engl J Med* 2012; 367:197-198.
3. Harkness EF, Macfarlane GJ, Silman AJ, McBeth J. Is musculoskeletal pain more common now than 40 years ago?: Two population-based cross-sectional studies. *Rheumatology (Oxford.* 2005; 44:890-895.
4. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, Castel LD, Kalsbeek WD, Carey TS. The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169:251-258.
5. Manchikanti L, Singh V, Datta S, Cohen SP, Hirsch JA. Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician* 2009; 12:E35-E70.
6. Hoy DG, Bain C, Williams G, March L, Brooks P, Blyth F, Woolf A, Vos T, Buchbinder R. A systematic review of the global prevalence of low back pain. *Arthritis Rheum.* 2012 Jan 9. [Epub ahead of print].
7. Hoy D, Brooks P, Blyth F, Buchbinder R. The epidemiology of low back pain. *Best Pract Res Clin Rheumatol* 2010; 24:769-781.
8. Hoy DG, Protani M, De R, Buchbinder R. The epidemiology of neck pain. *Best Pract Res Clin Rheumatol* 2010; 24:783-792.
9. Reid KJ, Harker J, Bala MM, Truyers C, Kellen E, Bekkering GE, Kleijnen J. Epidemiology of chronic non-cancer pain in Europe: Narrative review of prevalence, pain treatments and pain impact. *Curr Med Res Opin* 2011; 27:449-462.
10. Bekkering GE, Bala MM, Reid K, Kellen E, Harker J, Riemsma R, Huygen FJ, Kleijnen J. Epidemiology of chronic pain and its treatment in The Netherlands. *Neth J Med* 2011; 69:141-153.
11. Langley PC. The prevalence, correlates and treatment of pain in the European Union. *Curr Med Res Opin* 2011; 27:463-480.
12. Tosato M, Lukas A, van der Roest HG, Danese P, Antocicco M, Finne-Soveri H,

Nikolaus T, Landi F, Bernabei R, Onder G. Association of pain with behavioral and psychiatric symptoms among nursing home residents with cognitive impairment: Results from the SHELTER study. *Pain* 2012; 153:305-310.

13. Clark JD. Chronic pain prevalence and analgesic prescribing in a general medical population. *J Pain Symptom Manage* 2002; 23:131-137.
14. Eriksen J. Epidemiology of chronic nonmalignant pain in Denmark. *Pain* 2003; 106:221-228.
15. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. *JAMA* 1998; 280:147-151.
16. Moulin DE, Clark AJ, Speechley M, Morley-Forster PK. Chronic pain in Canada – prevalence, treatment, impact and the role of opioid analgesia. *Pain Res Manag* 2002; 7:179-184.
17. Sjøgren P, Ekholm O, Peuckmann V, Grønbæk M. Epidemiology of chronic pain in Denmark: an update. *Eur J Pain* 2009; 13:287-292.
18. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet* 1999; 354:1248-1252.
19. Eriksen J, Ekholm O, Sjøgren P, Rasmussen NK. Development of and recovery from long-term pain. A 6-year follow-up study of a cross-section of the adult Danish population. *Pain* 2004; 108:154-162.
20. Lawrence RC, Helmick CG, Arnett FC. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998; 41:778-799.
21. Verhaak PF, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: a review of the literature. *Pain* 1998; 77:231-239.
22. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain* 2006; 7:281-289.
23. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; 10:287-333.
24. Blyth FM, Rochat S, Cumming RG, Creasey H, Handelsman DJ, Le Couteur DG, Naganathan V, Sambrook PN, Seibel MJ, Waite LM. Pain, frailty and comorbidity on older men: the CHAMP study. *Pain* 2008; 140:224-230.
25. Cassidy JD, Carroll LJ, Côté P. The Saskatchewan Health and Back Pain Survey. The prevalence of low back pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1860-1867.
26. Côté P, Cassidy JD, Carroll L. The Saskatchewan Health and Back Pain Survey. The prevalence of neck pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1689-1698.
27. Leboeuf-Yde C, Nielsen J, Kyvik KO, Fejer R, Hartvigsen J. Pain in the lumbar, thoracic or cervical regions: Do age or gender matter? A population-based study of 34,902 Danish twins 20-71 years of age. *BMC Musculoskeletal Disorders* 2009; 39.
28. Carroll LJ, Cassidy JD, Peloso PM, Giles-Smith L, Cheng CS, Greenhalgh SW, Haldeman S, van der Velde G, Hurwitz EL, Côté P, Nordin M, Hogg-Johnson S, Holm LW, Guzman J, Carragee EJ. Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. The burden and determinants of neck pain in the general population: Results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and its associated disorders. *Spine (Phila Pa 1976)* 2008; 33:S39-S51.
29. Côté P, Kristman V, Vidmar M, Van Eerd D, Hogg-Johnson S, Beaton D, Smith PM. The prevalence and incidence of work absenteeism involving neck pain: a cohort of Ontario lost-time claimants. *Spine (Phila Pa 1976)* 2008; 33:S192-S198.
30. Côté P, Cassidy JD, Carroll L. The factors associated with neck pain and its related disability in the Saskatchewan population. *Spine (Phila Pa 1976)* 2000; 25:1109-1117.
31. Deyo RA, Smith DH, Johnson ES, Donovan M, Tillotson CJ, Yang X, Petrik AF, Dobscha SK. Opioids for back pain patients: Primary care prescribing patterns and use of services. *J Am Board Fam Med* 2011; 24:717-727.
32. Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: A ten-year perspective. *Pain Physician* 2010; 13:401-435.
33. Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: An epidemiological study. *Pain* 2006; 125:172-179.
34. Centers for Disease Control and Prevention. CDC grand rounds: Prescription drug overdoses – a U.S. epidemic. *MMWR Morb Mortal Wkly Rep* 2012; 61:10-13.
35. Manchikanti L, Benyamin R, Datta S, Vallejo R, Smith HS. Opioids in chronic noncancer pain. *Expert Rev Neurother* 2010; 10:775-789.
36. Ballantyne J, LaForge K. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain* 2007; 129:235-255.
37. US Government Accountability Office: Report to Congressional Requesters. Prescription Pain Reliever Abuse, December 2011. www.gao.gov/assets/590/587301.pdf
38. Toblin RL, Mack KA, Perveen G, Paulozzi LJ. A population-based survey of chronic pain and its treatment with prescription drugs. *Pain* 2011; 152:1249-1255.
39. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med* 2010; 363:1981-1985.
40. Martin BI, Turner JA, Mirza SK, Lee MJ, Comstock BA, Deyo RA. Trends in health care expenditures, utilization, and health status among US adults with spine problems, 1997-2006. *Spine (Phila Pa 1976)* 2009 34:2077-2084.
41. Webster LR. Ending unnecessary opioid-related deaths: A national priority. *Pain Med* 2011; 12:S13-S15.
42. Collen M. Profit-Driven Drug Testing. *J Pain Palliat Care Pharmacother* 2012; 26:13-17.
43. Braden JB, Russo J, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med* 2010; 170:1425-1432.
44. Volkow ND, McLellan TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *JAMA* 2011; 305:1346-1347.
45. Paulozzi LJ, Kilbourne EM, Shah NG, Nolte KB, Desai HA, Landen MG, Harvey W, Loring LD. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Med* 2012; 13:87-95.
46. Cicero TJ, Wong G, Tian Y, Lynskey M, Todorov A, Isenberg K. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: Data from an insurance claims database. *Pain* 2009; 144:20-27.

47. Lavin R, Park J. Depressive symptoms in community-dwelling older adults receiving opioid therapy for chronic pain. *J Opioid Manag* 2011; 7:309-319.
48. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *J Bone Joint Surg Am* 2009; 91:919-927.
49. Sjøgren P, Grønbæk M, Peuckmann V, Ekholm O. A population-based cohort study on chronic pain: the role of opioids. *Clin J Pain* 2010; 26:763-769.
50. Fauber J. Painkiller boom fueled by networking. *Journal Sentinel*, Feb. 18, 2012.
51. Murnion BP, Gnjidic D, Hilmer SN. Prescription and administration of opioids to hospital in-patients, and barriers to effective use. *Pain Med* 2010; 11:58-66.
52. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003; 97:534-540.
53. Dix P, Sandhar B, Murdoch J, MacIntyre PA. Pain on medical wards in a district general hospital. *Br J Anaesth* 2004; 92:235-237.
54. Brown D, McCormack B. Determining factors that have an impact upon effective evidence-based pain management with older people, following colorectal surgery: An ethnographic study. *J Clin Nurs* 2006; 15:1287-1298.
55. Ljungberg C, Lindblad AK, Tully MP. Hospital doctors' views of factors influencing their prescribing. *J Eval Clin Pract* 2007; 13:765-771.
56. Auret K, Schug SA. Underutilisation of opioids in elderly patients with chronic pain: Approaches to correcting the problem. *Drugs Aging* 2005; 22:641-654.
57. McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: Pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther* 2001; 8:181-186.
58. McErlean M, Triner W, Young A. Impact of outside regulatory investigation on opiate administration in the emergency department. *J Pain* 2006; 7:947-950.
59. Gnjidic D, Murnion BP, Hilmer SN. Age and opioid analgesia in an acute hospital population. *Age Ageing* 2008; 37(6):699-702.
60. Ensuring availability of controlled medications for the relief of pain and preventing diversion and abuse: Striking the right balance to achieve the optimal public health outcome. Discussion paper based on a scientific workshop, January 18-19, 2011, UNODC, Vienna.
61. International Narcotics Control Board, Report of the International Narcotics Control Board on the availability of internationally controlled drugs: Ensuring adequate access for medical and scientific purposes. New York 2011.
62. Nicholson BD. Panel Discussion. *Pain Med* 2012; 13:S21-S22.
63. Nicholson BD. Introduction. *Pain Med* 2012; 13:S1-S3.
64. A fresh view of opioids. *The BackLetter* 2011; 26:4, 37.
65. Federation of State Medical Boards of the US. Model guidelines for the use of controlled substances for the treatment of pain: A policy document of the Federation of State Medical Boards of the United States, Inc. Dallas, TX, 1998.
66. Phillips DM. JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations. *JAMA* 2000; 284:428-429.
67. Cohen MZ, Easley MK, Ellis C, Hughes B, Ownby K, Rashad BG, Rude M, Taft E, Westbrooks JB. JCAHO cancer pain management and the JCAHO's pain standards: An institutional challenge. *J Pain Symptom Manage* 2003; 25:519-527.
68. Frasco PE, Sprung J, Trentman TL. The impact of the Joint Commission for Accreditation of Healthcare Organizations pain initiative on perioperative opiate consumption and recovery room length of stay. *Anesth Analg* 2005; 100:162-168.
69. Tormoehlen LM, Mowry JB, Bodle JD, Rusyniak DE. Increased adolescent opioid use and complications reported to a poison control center following the 2000 JCAHO pain initiative. *Clin Toxicol (Phila)* 2011; 49:492-498.
70. Mularski RA, White-Chu F, Overbay D, Miller L, Asch SM, Ganzini L. Measuring pain as the 5th vital sign does not improve quality of pain management. *J Gen Intern Med* 2006; 21:607-612.
71. Letter to Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, U.S Food and Drug Administration, from Physicians for Responsible Opioid Prescribing RE Docket No. FDA-2011-D-0771, Draft Blueprint for Prescriber Education for Long-Acting/Extended Release Opioid Class-Wide Risk Evaluation and Mitigation Strategies. 2 December, 2011.
72. Nickerson JW, Attaran A. The inadequate treatment of pain: collateral damage from the war on drugs. *PLoS Med* 2012; 9:e1001153.
73. Small D, Drucker E. Return to Galileo? The Inquisition of the International Narcotic Control Board. *Harm Reduct J* 2008; 5:16.
74. Gilson AM, Joranson DE, Maurer MA. Improving state pain policies: recent progress and continuing opportunities. *CA Cancer J Clin* 2007; 57:341-353.
75. Gilson AM, Maurer MA, Joranson DE. State medical board members' beliefs about pain, addiction, and diversion and abuse: A changing regulatory environment. *J Pain* 2007; 8:682-691.
76. Taylor AL. Addressing the global tragedy of needless pain: Rethinking the United Nations single convention on narcotic drugs. *J Law Med Ethics* 2007; 35:556-570, 511.
77. Lipman AG. Pain as a human right: The 2004 Global Day Against Pain. *J Pain Palliat Care Pharmacother* 2005; 19:85-100.
78. Dilcher AJ. Damned if they do, damned if they don't: The need for a comprehensive public policy to address the inadequate management of pain. *Ann Health Law* 2004; 13:81-144, table of contents.
79. Ghodse H. Pain, anxiety and insomnia--a global perspective on the relief of suffering: Comparative review. *Br J Psychiatry* 2003; 183:15-21.
80. Gostomzyk JG, Heller WD. Prescribing strong opioids for pain therapy and for substitution therapy by established physicians. *Schmerz* 1996; 10:292-298.
81. Lohman D, Schleifer R, Amon JJ. Access to pain treatment as a human right. *BMC Med* 2010; 8:8.
82. Inadequate pain treatment is a public health crisis. Drug war shouldn't claim new victims. *StarTribune*, April 21, 2011. www.startribune.com/opinion/editorials/120420264.html
83. Canadian groups welcome international report condemning failed "War On Drugs." June 2, 2011. www.aidslaw.ca/publications/interfaces/downloadFile.php?ref=1886
84. [No authors listed]. Pain management failing as fears of prescription drug abuse rise. *J Pain Palliat Care Pharmacother* 2010; 24:182-183.
85. Varrassi G, Müller-Schwefe GH. The international CHANGE PAIN Physician Survey: Does specialism influence the

perception of pain and its treatment? *Curr Med Res Opin* 2012; Mar 28 [Epub ahead of print].

86. War on Drugs. Report of the Global Commission on Drug Policy. June 2011. www.globalcommissionondrugs.org/reports/
87. Milani B, Scholten W. World Health Organization. The World Medicines Situation 2011: Access to Controlled Medicines. http://apps.who.int/medicinedocs/documents/s18062en/s18062en.pdf
88. Dasgupta N, Mandl K, Brownstein J. Breaking the news or fueling the epidemic? Temporal association between news media report volume and opioid-related mortality. *PLoS ONE* 2009; 4:e7758.
89. Are we winning the war on drugs? Is it worth the cost? *MD Health Network*. www.mdhealthnetwork.org/prescription-drugs/war_on_drugs.html
90. Painful drug war victory. *The Washington Times*. August 16, 2007. www.washingtontimes.com/news/2007/aug/16/painful-drug-war-victory/?page=all
91. Fauber J. UW a force in pain drug growth. *JSOnline*. 2 April, 2011.
92. Fauber J. Academics profit by making the case for opioid painkillers. *MedPage Today*. 3 April, 2011.
93. Manchikanti L, Benyamin RM, Falco FJE, Caraway DL, Datta S, Hirsch JA. Guidelines warfare over interventional techniques: Is there a lack of discourse or straw man? *Pain Physician* 2012; 15:E1-E26.
94. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: Report of 38 cases. *Pain* 1986; 25:171-186.
95. Ballantyne JC. Opioid analgesia: Perspectives on right use and utility. *Pain Physician* 2007; 10:479-491.
96. Chou R, Huffman L. *Use of Chronic Opioid Therapy in Chronic Noncancer Pain: Evidence Review*. American Pain Society; Glenview, IL: 2009.

www.ampainsoc.org/pub/pdf/Opioid_Final_Evidence_Report.pdf

97. Hill CS. Government regulatory influences on opioid prescribing and their impact on the treatment of pain of nonmalignant origin. *J Pain Symptom Manage* 1996; 11:287-298.
98. The American Academy of Pain Medicine, the American Pain Society. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain* 1997; 13:6-8.
99. Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain* 2008; 24:497-508.
100. Manchikanti L, Ailinani H, Koyyalagunta D, Datta S, Singh V, Eriator I, Sehgal N, Shah RV, Benyamin RM, Vallejo R, Fellows B, Christo PJ. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain Physician* 2011; 14:91-121.
101. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, Schoelles KM. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev* 2010; 1:CD006605.
102. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain* 2004; 112:372-380.
103. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. *Can Med Assoc J* 2006; 174:1589-1594.
104. Eisenberg E, McNicol E, Carr DB. Opioids for neuropathic pain (review). *Cochrane Database Syst Rev* 2006, 3:CD006146.
105. Deshpande A, Furlan A, Mailis-Gagnon A, Atlas S, Turk D. Opioids for chronic low back pain (review). *Cochrane Database Syst Rev* 2007; 3:CD004959.
106. Devulder J, Richarz U, Nataraja SH. Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Curr Med Res Opin* 2005; 21:1555-1568.
107. Manchikanti L, Vallejo R, Manchikanti KN, Benyamin RM, Datta S, Christo PJ. Effectiveness of long-term opioid therapy for chronic non-cancer pain. *Pain Physician* 2011; 14:E133-E156.
108. Colson J, Koyyalagunta D, Falco FJE, Manchikanti L. A systematic review of observational studies on the effectiveness of opioid therapy for cancer pain. *Pain Physician* 2011; 14:E85-E102.
109. Vallejo R, Barkin RL, Wang VC. Pharmacology of opioids in the treatment of chronic pain syndromes. *Pain Physician* 2011; 14:E343-E360.
110. Trescot AM, Helm S, Hansen H, Benyamin R, Adlaka R, Patel S, Manchikanti L. Opioids in the management of chronic non-cancer pain: An update of American Society of Interventional Pain Physicians' (ASIPP) guidelines. *Pain Physician* 2008; 11:S5-S62.
111. Stein C, Reinecke H, Sorgatz H. Opioid use in chronic noncancer pain: Guidelines revisited. *Curr Opin Anaesthesiol* 2010; 23:598-601.
112. von Korff M, Kolodny A, Deyo R, Chou R. Long-term opioid therapy reconsidered. *Ann Intern Med* 2011; 155:325-328.
113. Grady D, Berkowitz SA, Katz MH. Opioids for chronic pain. *Arch Intern Med* 2011; 171:1426-1427.
114. Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. *BMJ* 2011; 343:d5142.
115. Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, Fiellin DA. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. *Ann Intern Med* 2007; 146:116-127.
116. Who bears responsibility for the premature adoption of opioids as a treatment standard? *The Back Letter* 2011; 26:46
117. Chou R, Huffman LH; American Pain Society; American College of Physicians. Medications for acute and chronic low back pain: A review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007; 147:505-514.
118. Reinecke H, Sorgatz H; German Society for the Study of Pain (DGSS). S3 guideline LONTS. Long-term administration of opioids for non-tumor pain. *Schmerz* 2009; 23:440-447.
119. Sorgatz H, Maier C. Nothing is more damaging to a new truth than an old error: Conformity of new guidelines on opioid administration for chronic pain with the effect prognosis of the DGSS S3 guidelines LONTS (long-term administration of opioids for non-tumor pain). *Schmerz* 2010; 24:309-312.
120. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006; 104:570-587.
121. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011; 14:145-161.
122. Cohen SP, Christo PJ, Wang S, Chen L, Stojanovic MP, Shields CH, Brummett C, Mao J. The effect of opioid dose and treatment duration on the perception of

a painful standardized clinical stimulus. *Reg Anesth Pain Med* 2008; 33:199-206.

123. Raffaelli W, Salmosky-Dekel BG. Biological consequences of long-term intrathecal administration of opioids. *Minerva Anestesiol* 2005; 71:475-478.

124. Deer TR, Smith HS, Burton AW, Pope JE, Doleys DM, Levy RM, Staats PS, Wallace MS, Webster LR, Rauck RL, Cousins M. Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. *Pain Physician* 2011; 14:E283-E312.

125. Edlund MJ, Martin BC, Devries A, Fan M-Y, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP Study. *Clin J Pain* 2010; 26:1-8.

126. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: the TROUP Study. *Pain* 2010; 150:332-339.

127. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain* 2007; 8:573-582.

128. Sullivan MD. Limiting the potential harms of high-dose opioid therapy: Comment on "Opioid dose and drug-related mortality in patients with nonmalignant pain." *Arch Intern Med* 2011; 171:691-693.

129. Katz MH. Long-term opioid treatment of nonmalignant pain: a believer loses his faith. *Arch Intern Med* 2010; 170:1422-1424.

130. McLellan AT, Turner BJ. Chronic noncancer pain management and opioid overdose: Time to change prescribing practices. *Ann Intern Med* 2010; 152:123-124.

131. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med* 2010; 152:85-92.

132. Manchikanti L, Singh V, Caraway DL, Benyamin RM. Breakthrough pain in chronic non-cancer pain: Fact, fiction, or abuse. *Pain Physician* 2011; 14:E103-E117.

133. Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, Braden JB, Psaty BM, Von Korff M. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med* 2010; 25:310-315.

134. Walker JM, Farney RJ, Rhondeau SM, Boyle KM, Valentine K, Cloward TV, Shilling KC. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med* 2007; 3:455-461.

135. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med* 2010; 170:1968-1976.

136. Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med* 2011; 26:1450-1457.

137. Pletcher MJ, Kertesz SG, Kohn MA, Gonzales. R. Trends in opioid prescribing by race/ethnicity for patients seeking care in US emergency departments. *JAMA* 2008; 299:70-78.

138. American Society for Pain Management Nursing (ASPMN); Emergency Nurses Association (ENA); American College of Emergency Physicians (ACEP); American Pain Society (APS). Policy statement. Optimizing the treatment of pain in patients with acute presentations. *Ann Emerg Med* 2010; 56:77-79.

139. American College of Emergency Physicians. Policy statement. Electronic prescription monitoring. Approved by the ACEP Board of Directors, October 2011. *Ann. Emerg. Med.* Pending publication, March 2012.

140. Department of Health and Human Services, Food and Drug Administration. Draft blueprint for prescriber education for long-acting/extended-release opioid class-wide risk evaluation and mitigation strategy. *Fed. Reg.* 76, 68766-68767 (November 7, 2011).

141. Solanki DR, Koyyalagunta D, Shah RV, Silverman SM, Manchikanti L. Monitoring opioid adherence in chronic pain patients: Assessment of risk of substance misuse. *Pain Physician* 2011; 14:E119-E131.

142. Christo PJ, Manchikanti L, Ruan X, Bottros M, Hansen H, Solanki D, Jordan AE, Colson J. Urine drug testing in chronic pain. *Pain Physician* 2011; 14:123-143.

143. Gilbert JW, Wheeler GR, Mick GE, Storey BB, Herder SL, Richardson GB, Watts E, Gyarteng-Dakwa K, Marino BS, Kenney CM, Siddiqi M, Broughton PG. Importance of urine drug testing in the treatment of chronic noncancer pain: Implications of recent medicare policy changes in Kentucky. *Pain Physician* 2010; 13:167-186.

144. Gilbert JW, Wheeler GR, Mick GE, Storey BB, Herder SL, Richardson GB, Watts E, Gyarteng-Dakwa K, Marino BS, Kenney CM, Siddiqi M, Broughton PG. Urine drug testing in the treatment of chronic noncancer pain in a Kentucky private neuroscience practice: The potential effect of Medicare benefit changes in Kentucky. *Pain Physician* 2010; 13:187-194.

145. Manchikanti L, Malla Y, Wargo BW, Fellows B. Comparative evaluation of the accuracy of immunoassay with liquid chromatography tandem mass spectrometry (LC/MS/MS) of urine drug testing (UDT) opioids and illicit drugs in chronic pain patients. *Pain Physician* 2011; 14:175-187.

146. Manchikanti L, Malla Y, Wargo BW, Fellows B. Comparative evaluation of the accuracy of benzodiazepine testing in chronic pain patients utilizing immunoassay with liquid chromatography tandem mass spectrometry (LC/MS/MS) of urine drug testing. *Pain Physician* 2011; 14:259-270.

147. Pesce A, West C, West R, Crews B, Mikel C, Almazan P, Latyshev S, Rosenthal M, Horn P. Reference intervals: a novel approach to detect drug abuse in a pain patient population. *J Opioid Manage* 2010; 6:341-350.

148. Pesce A, Rosenthal M, West R, West C, Mikel C, Almazan P, Latyshev S. An evaluation of the diagnostic accuracy of liquid chromatography-tandem mass spectrometry versus immunoassay drug testing in pain patients. *Pain Physician* 2010; 13:273-281.

149. Manchikanti L, Malla Y, Wargo BW, Cash KA, Pampati V, Damron KS, McManus CD, Brandon DE. Protocol for accuracy of point of care (POC) or in-office urine drug testing (immunoassay) in chronic pain patients: A prospective analysis of immunoassay and liquid chromatography tandem mass spectometry (LC/MS/MS). *Pain Physician* 2010; 13:E1-E22.

150. McCarberg BH. A critical assessment of opioid treatment adherence using urine drug testing in chronic pain management. *Postgrad Med* 2011; 123:124-131.

151. Ling W, Mooney L, Hillhouse M. Prescription opioid abuse, pain and addiction: Clinical issues and implications. *Drug Alcohol Rev* 2011; 30:300-305.

152. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, Crosby AE, Paulozzi LJ. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA* 2008; 300:2613-2620.

153. United States Department of Justice, Drug Enforcement Administration. Automation of Reports and Consolidated Orders System (ARCOS). Springfield, VA, 2011.
www.deadiversion.usdoj.gov/arcos/index.html.

154. Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, Crosby AE. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. *Addiction* 2009; 104:1541-1548.

155. Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ* 2009; 181:891-896.

156. Toblin RL, Paulozzi LJ, Logan JE, Hall AJ, Kaplan JA. Mental illness and psychotropic drug use among prescription drug overdose deaths: A medical examiner chart review. *J Clin Psychiatry* 2010; 71:491-496.

157. Methadone Mortality Working Group Drug Enforcement Administration, Office of Diversion Control, April 2007.
www.deadiversion.usdoj.gov/drugs_concern/methadone/methadone_presentation0407_revised.pdf

158. Xu J, Kochanek KD, Murphy SL, Tejada-Vera B. Deaths: Final data for 2007. National vital statistics reports; Vol. 58 No. 19. National Center for Health Statistics, Hyattsville, MD, 2010.
http://www.cdc.gov/nchs/data/nvsr/nvsr58/nvsr58_01.pdf.

159. Warner M, Chen LH, Makuc DM, Anderson RN, Miniño AM. Drug poisoning deaths in the United States, 1980-2008. NCHS data brief, no. 81. National Center for Health Statistics, Hyattsville, MD, 2011.

160. Centers for Disease Control and Prevention. Vital signs: Overdoses of prescription opioid pain relievers – United States, 1999-2008. *MMWR. Morb Mortal Wkly Rep* 2011; 60:1487-1492.

161. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet* 2012; 379:55-70.

162. National Health Services, The National Treatment Agency for Substance Misuse. Addiction to Medicine. An investigation into the configuration and commissioning of treatment services to support those who develop problems with prescription-only or over-the-counter medicine. May 2011. www.nta.nhs.uk/uploads/addictiontomedicinesmay2011a.pdf

163. Wunsch MJ, Nakamoto K, Behonick G, Massello W. Opioid deaths in rural Virginia: A description of the high prevalence of accidental fatalities involving prescribed medications. *Am J Addict* 2009; 18:5-14.

164. Hudson TJ, Edlund MJ, Steffick DE, Tripathi SP, Sullivan MD. Epidemiology of regular prescribed opioid use: Results from a national, population-based survey. *J Pain Sympt Mgmt* 2008; 36:280-288.

165. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain* 2004; 109:514-519.

166. Franklin GM, Mai J, Wickizer T, Turner JA, Fulton-Kehoe D, Grant L. Opioid dosing trends and mortality in Washington State workers' compensation, 1996–2002. *Am J Ind Med* 2005; 48:91-99.

167. Luo X, Pietrobon R, Hey L. Patterns and trends in opioid use among individuals with back pain in the United States. *Spine (Phila Pa 1976)* 2004; 29:884-891.

168. Zerzan JT, Morden NE, Soumerai S, Ross-Degnan D, Roughead E, Zhang F, Simoni-Wastila L, Sullivan SD. Trends and geographic variation of opiate medication use in state Medicaid fee-for-service programs, 1996 to 2002. *Med Care* 2006; 44:1005-1010.

169. Manchikanti L, Pampati S, Damron KS, Cash KA, McManus CD, Fellows B. Identification of doctor shoppers with KASPER: A comparative evaluation over a decade in western Kentucky. *J Ky Med Assoc* 2012; in press.

170. Substance Abuse and Mental Health Services Administration. *Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings.* NSDUH Series H-41, HHS Publication No. (SMA) 11-4658. Substance Abuse and Mental Health Services Administration, Rockville, MD, 2011.
www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf.

171. Substance Abuse and Mental Health Services Administration. *Results from the 2010 National Survey on Drug Use and Health: Mental Health Findings.* NSDUH Series H-42, HHS Publication No. (SMA) 11-4667. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2012. www.samhsa.gov/data/NSDUH/2k10MH_Findings/2k10MHResults.pdf

172. Volkow ND, McLellan TA, Cotto JH. Characteristics of opioid prescriptions in 2009. *JAMA* 2011; 305:1299-1301.

173. Governale L. Outpatient prescription opioid utilization in the U.S., years 2000 – 2009. Drug Utilization Data Analysis Team Leader, Division of Epidemiology, Office of Surveillance and Epidemiology. Presentation for U.S. Food and Drug Administration, July 22, 2010.
www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM220950.pdf

174. Source: SDI, Vector One ®: National.

175. IMS Institute for Healthcare Informatics. The use of medicines in the United States: Review of 2011. April 2012.
www.imshealth.com/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S._Report_2011.pdf

176. Ricks D. UN: US consumes 80% of world's oxycodone. *Newsday*, January 21, 2012.

177. Report of the International Narcotics Control Board for 2004. New York, United Nations, 2005.
www.incb.org/pdf/e/ar/2004/incb_report_2004_full.pdf

178. Report of the International Narcotics Control Board 2008. New York, United Nations, 2009.
www.incb.org/pdf/annual-report/2008/en/AR_08_English.pdf

179. National Center for Health Statistics. Health, United States, 2008 with chartbook. National Center for Health Statistics, Hyattsville, MD, 2009.

180. Centers for Disease Control and Prevention. Adult use of prescription opioid pain medications – Utah, 2008. *MMWR Morb Mortal Wkly Rep* 2010; 59:153-157.

181. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000-2005 in commercial and Medicaid insurance plans: the TROUP study. *Pain* 2008; 138:440-449.

182. Vogt MT, Kwoh CK, Cope DK, Osial TA,

Culyba M, Starz TW. Analgesic usage for low back pain: Impact on health care costs and service use. *Spine (Phila Pa 1976)* 2005; 30:1075-1081.

183. Manchikanti L, Damron KS, McManus CD, Barnhill RC. Patterns of illicit drug use and opioid abuse in patients with chronic pain at initial evaluation: a prospective, observational study. *Pain Physician* 2004; 7:431-437.
184. Manchikanti L, Pampati V, Damron KS, Beyer CD, Barnhill RC, Fellows B. Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. *J KY Med Assoc* 2003; 101:511-517.
185. Manchikanti L, Damron KS, Pampati V, McManus CD. Prevalence of illicit drug use among individuals with chronic pain in the Commonwealth of Kentucky: an evaluation of patterns and trends. *J KY Med Assoc* 2005; 103:55-62.
186. Vaglienti RM, Huber SJ, Noel KR, Johnstone RE. Misuse of prescribed controlled substances defined by urinalysis. *WV Med J* 2003; 99:67-70.
187. Michna E, Jamison RN, Pham LD, Ross EL, Janfaza D, Nedeljkovic SS, Narang S, Palombi D, Wasan AD. Urine toxicology screening among chronic pain patients on opioid therapy: Frequency and predictability of abnormal findings. *Clin J Pain* 2007; 23:173-179.
188. Manchikanti L, Manchukonda R, Pampati V, Damron KS, Brandon DE, Cash KA, McManus CD. Does random urine drug testing reduce illicit drug use in chronic pain patients receiving opioids? *Pain Physician* 2006; 9:123-129.
189. Wu PC, Lang C, Hasson NK, Linder SH, Clark DJ. Opioid use in young veterans. *J Opioid Manag* 2010; 6:133-139.
190. Unintentional Drug Poisoning in the United States. Centers for Disease Control and Prevention. July 2010. http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf
191. Paulozzi LJ, Weisler RH, Patkar AA. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. *J Clin Psychiatry* 2011; 72:589-592.
192. Ohio Department of Health. Epidemic of prescription drug overdose in Ohio. 2010. www.healthyohioprogram.org/diseaseprevention/dpoison/drugdata.aspx.
193. Edlund MJ, Martin BC, Fan MY, Braden JB, Devries A, Sullivan MD. An analysis of heavy utilizers of opioids for chronic noncancer pain in the TROUP study. *J Pain Symptom Manage* 2010; 40:279-289.
194. Katz N, Panas L, Kim M, Audet AD, Bilansky A, Eadie J, Kreiner P, Paillard FC, Thomas C, Carrow G. Usefulness of prescription monitoring programs for surveillance--analysis of Schedule II opioid prescription data in Massachusetts, 1996-2006. *Pharmacoepidemiol Drug Saf* 2010; 19:115-123.
195. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 2011; 305:1315-1321.
196. Lanier WA. Prescription drug overdose deaths – Utah, 2008-2009. *In Proceedings at the 59th Annual Epidemic Intelligence Service Conference.* Atlanta, GA, April 23, 2010.
197. Manchikanti L, Singh V, Boswell MV. Interventional pain management at crossroads: The perfect storm brewing for a new decade of challenges. *Pain Physician* 2010; 13:E111-E140.
198. Benyamin RM, Datta S, Falco FJE. A perfect storm in interventional pain management: Regulated, but unbalanced. *Pain Physician* 2010; 13:109-116.
199. Office of National Drug Control Policy. 2011 National Drug Control Strategy. http://www.whitehouse.gov/ondcp/2011-national-drug-control-strategy
200. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. A randomized, controlled, double-blind trial of fluoroscopic caudal epidural injections in the treatment of lumbar disc herniation and radiculitis. *Spine (Phila Pa 1976)* 2011; 36:1897-1905.
201. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Management of pain of post lumbar surgery syndrome: One-year results of a randomized, double double-blind, active controlled trial of fluoroscopic caudal epidural injections. *Pain Physician* 2010; 13:509-521.
202. Manchikanti L, Cash RA, McManus CD, Pampati V, Fellows B. Fluoroscopic caudal epidural injections with or without steroids in managing pain of lumbar spinal stenosis: One year results of randomized, double-blind, active-controlled trial. *J Spinal Disord* 2011; April 5 [Epub ahead of print].
203. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. Preliminary results of a randomized, double-blind, controlled trial of fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation or radiculitis. *Pain Physician* 2010; 13:E279-E292.
204. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJE. Lumbar interlaminar epidural injections in central spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:51-64.
205. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic epidural injections in cervical spinal stenosis: Preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; 15:E59-E70.
206. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic cervical interlaminar epidural injections in managing chronic pain of cervical post-surgery syndrome: Preliminary results of a randomized, double-blind active control trial. *Pain Physician* 2012; 15:13-26.
207. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. A preliminary report of a randomized double-blind, active controlled trial of fluoroscopic thoracic interlaminar epidural injections in managing chronic thoracic pain. *Pain Physician* 2010; 13:E357-E369.
208. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of lumbar facet joint nerve blocks in managing chronic low back pain: a randomized, double-blind, controlled trial with a 2-year follow-up. *Int J Med Sci* 2010; 7:124-135.
209. Manchikanti L, Singh V, Falco FJE, Cash KA, Fellows B. Comparative outcomes of a 2-year follow-up of cervical medial branch blocks in management of chronic neck pain: a randomized, double-blind controlled trial. *Pain Physician* 2010; 13:437-450.
210. Chou R, Huffman L. *Guideline for the Evaluation and Management of Low Back Pain: Evidence Review.* American Pain Society, Glenview, IL, 2009. www.ampainsoc.org/pub/pdf/LBPEvidRev.pdf.
211. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V, Fellows B. Comparative effectiveness of a one-year follow-up of thoracic medial branch blocks in management of chronic thoracic pain: a randomized, double-blind active controlled trial. *Pain Physician* 2010; 13:535-548.
212. Staal JB, de Bie RA, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy

for subacute and chronic low back pain: an updated Cochrane review. *Spine (Phila Pa 1976)* 2009; 34:49-59.

213. American College of Occupational and Environmental Medicine (ACOEM) Low back Disorders. In: *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery of Workers, Second Edition.* American College of Occupational and Environmental Medicine Press, Elk Grove Village, 2007.
214. Manchikanti L, Datta S, Derby R, Wolfer LR, Benyamin RM, Hirsch JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 1. Diagnostic interventions. *Pain Physician* 2010; 13:E141-E174.
215. Manchikanti L, Datta S, Gupta S, Munglani R, Bryce DA, Ward SP, Benyamin RM, Sharma ML, Helm II S, Fellows B, Hirsch JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 2. Therapeutic interventions. *Pain Physician* 2010; 13:E215-E264.
216. Manchikanti L, Manchukonda R, Pampati V, Damron KS. Evaluation of abuse of prescription and illicit drugs in chronic pain patients receiving short-acting (hydrocodone) or long-acting (methadone) opioids. *Pain Physician* 2005; 8:257-261.
217. Macintyre PE, Loadsman JA, Scott DA. Opioids, ventilation and acute pain management. *Anaesth Intensive Care* 2011; 39:545-558.
218. Webster LR, Cochella S, Dasgupta N, Fakata KL, Fine PG, Fishman SM, Grey T, Johnson EM, Lee LK, Passik SD, Peppin J, Porucznik CA, Ray A, Schnoll SH, Stieg RL, Wakeland W. An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Med* 2011; 12:S26-S35.
219. Perrin-Terrin A, Pathak A, Lapeyre-Mestre M. QT interval prolongation: Prevalence, risk factors and pharmacovigilance data among methadone-treated patients in France. *Fundam Clin Pharmacol* 2011; 25:503-510.
220. Anchersen K, Hansteen V, Gossop M, Clausen T, Waal H. Opioid maintenance patients with QTc prolongation: Congenital long QT syndrome mutation may be a contributing risk factor. *Drug Alcohol Depend* 2010; 112:216-219.
221. Modesto-Lowe V, Brooks D, Petry N. Methadone deaths: Risk factors in pain and addicted populations. *J Gen Intern Med* 2010; 25:305-309.
222. Mayet S, Gossop M, Lintzeris N, Markides V, Strang J. Methadone maintenance, QTc and torsade de pointes: Who needs an electrocardiogram and what is the prevalence of QTc prolongation? *Drug Alcohol Rev* 2011; 30:388-396.
223. Manchikanti L, Damron KS, Beyer CD, Pampati V. A comparative evaluation of illicit drug use in patients with or without controlled substance abuse in interventional pain management. *Pain Physician* 2003; 6:281-285.
224. Fillingim RB, Doleys DM, Edwards RR, Lowery D. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. *Spine (Phila Pa 1976)* 2003; 28:143-150.
225. Webster BS, Verma SK, Gatchel RJ. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery, and late opioid use. *Spine (Phila Pa 1976)* 2007; 32:2127-2132.
226. Mahmud MA, Webster BS, Courtney TK, Matz S, Tacci JA, Christiani DC. Clinical management and the duration of disability for work-related low back pain. *J Occup Environ Med* 2000; 42:1178-1187.
227. Franklin GM, Stover BD, Turner JA, Fulton- Kehoe D, Wickizer TM; Disability Risk Identification Study Cohort. Early opioid prescription and subsequent disability among workers with back injuries: The Disability Risk Identification Study Cohort. *Spine (Phila Pa 1976)* 2008; 33:199-204.
228. Rhee Y, Taitel MS, Walker DR, Lau DT. Narcotic drug use among patients with lower back pain in employer health plans: a retrospective analysis of risk factors and health care services. *Clin Ther* 2007; 29:2603-2612.
229. Gross DP, Stephens B, Bhambhani Y, Haykowsky M, Bostick GP, Rashiq S. Opioid prescriptions in canadian workers' compensation claimants: Prescription trends and associations between early prescription and future recovery. *Spine (Phila Pa 1976)* 2009; 34:525-531.
230. Volinn E, Fargo JD, Fine PG. Opioid therapy for nonspecific low back pain and the outcome of chronic work loss. *Pain* 2009; 142:194-201.
231. Cifuentes M, Webster B, Genevay S, Pransky G. The course of opioid prescribing for a new episode of disabling low back pain: Opioid features and dose escalation. *Pain* 2010; 151:22-29.
232. Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. *Pain* 2000; 84:203-211.
233. Webster BS, Cifuentes M, Verma S, Pransky G. Geographic variation in opioid prescribing for acute, work-related, low back pain and associated factors: A multilevel analysis. *Am J Ind Med* 2009; 52:162-171.
234. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: a prospective, population-based study among injured workers in Washington state, 2002-2005. *Clin J Pain* 2009; 25:743-751.
235. Stover BD, Turner JA, Franklin G, Gluck JV, Fulton-Kehoe D, Sheppard L, Wickizer TM, Kaufman J, Egan K. Factors associated with early opioid prescription among workers with low back injuries. *J Pain* 2006; 7:718-725.
236. White AG, Birnbaum HG, Mareva MN, Daher M, Vallow S, Schein J, Katz N. Direct costs of opioid abuse in an insured population in the United States. *J Manag Care Pharm* 2005; 11:469-479.
237. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain* 1992; 8:77-85.

EXHIBIT B

Am J Public Health. 2009 February; 99(2): 221–227.
doi: 10.2105/AJPH.2007.131714
PMCID: PMC2622774

The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy

Art Van Zee, MD
Author information ▶ Article notes ▶ Copyright and License information ▶

Go to:

Abstract

I focus on issues surrounding the promotion and marketing of controlled drugs and their regulatory oversight. Compared with noncontrolled drugs, controlled drugs, with their potential for abuse and diversion, pose different public health risks when they are overpromoted and highly prescribed. An in-depth analysis of the promotion and marketing of OxyContin illustrates some of the associated issues.

Modifications of the promotion and marketing of controlled drugs by the pharmaceutical industry and an enhanced capacity of the Food and Drug Administration to regulate and monitor such promotion can have a positive impact on the public health.

CONTROLLED DRUGS, WITH their potential for abuse and diversion, can pose public health risks that are different from—and more problematic than—those of uncontrolled drugs when they are overpromoted and highly prescribed. An in-depth analysis of the promotion and marketing of OxyContin (Purdue Pharma, Stamford, CT), a sustained-release oxycodone preparation, illustrates some of the key issues. When Purdue Pharma introduced OxyContin in 1996, it was aggressively marketed and highly promoted. Sales grew from $48 million in 1996 to almost $1.1 billion in 2000.[1] The high availability of OxyContin correlated with increased abuse, diversion, and addiction, and by 2004 OxyContin had become a leading drug of abuse in the United States.[2]

Under current regulations, the Food and Drug Administration (FDA) is limited in its oversight of the marketing and promotion of controlled drugs. However, fundamental changes in the promotion and marketing of controlled drugs by the pharmaceutical industry, and an enhanced capacity of the FDA to regulate and monitor such promotion, can positively affect public health.

OxyContin's commercial success did not depend on the merits of the drug compared with other available opioid preparations. The *Medical Letter on Drugs and Therapeutics* concluded in 2001 that oxycodone offered no advantage over appropriate doses of other potent opioids.[3] Randomized double-blind studies comparing OxyContin given every 12 hours with immediate-release oxycodone given 4 times daily showed comparable efficacy and safety for use with chronic back pain[4] and cancer-related pain.[5,6] Randomized double-blind studies that compared OxyContin with controlled-release morphine for cancer-related pain also found comparable efficacy and safety.[7–9] The FDA's medical review officer, in evaluating the efficacy of OxyContin in Purdue's 1995 new drug application, concluded that OxyContin had not been shown to

have a significant advantage over conventional, immediate-release oxycodone taken 4 times daily other than a reduction in frequency of dosing.[10] In a review of the medical literature, Chou et al. made similar conclusions.[11]

The promotion and marketing of OxyContin occurred during a recent trend in the liberalization of the use of opioids in the treatment of pain, particularly for chronic non–cancer-related pain. Purdue pursued an "aggressive" campaign to promote the use of opioids in general and OxyContin in particular.[1,12–17] In 2001 alone, the company spent $200 million[18] in an array of approaches to market and promote OxyContin.

Go to:

PROMOTION OF OXYCONTIN

From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences at resorts in Florida, Arizona, and California. More than 5000 physicians, pharmacists, and nurses attended these all-expenses-paid symposia, where they were recruited and trained for Purdue's national speaker bureau.[19(p22)] It is well documented that this type of pharmaceutical company symposium influences physicians' prescribing, even though the physicians who attend such symposia believe that such enticements do not alter their prescribing patterns.[20]

One of the cornerstones of Purdue's marketing plan was the use of sophisticated marketing data to influence physicians' prescribing. Drug companies compile prescriber profiles on individual physicians—detailing the prescribing patterns of physicians nationwide—in an effort to influence doctors' prescribing habits. Through these profiles, a drug company can identify the highest and lowest prescribers of particular drugs in a single zip code, county, state, or the entire country.[21] One of the critical foundations of Purdue's marketing plan for OxyContin was to target the physicians who were the highest prescribers for opioids across the country.[1,12–17,22] The resulting database would help identify physicians with large numbers of chronic-pain patients. Unfortunately, this same database would also identify which physicians were simply the most frequent prescribers of opioids and, in some cases, the least discriminate prescribers.

A lucrative bonus system encouraged sales representatives to increase sales of OxyContin in their territories, resulting in a large number of visits to physicians with high rates of opioid prescriptions, as well as a multifaceted information campaign aimed at them. In 2001, in addition to the average sales representative's annual salary of $55 000, annual bonuses averaged $71 500, with a range of $15 000 to nearly $240 000. Purdue paid $40 million in sales incentive bonuses to its sales representatives that year.[19]

From 1996 to 2000, Purdue increased its internal sales force from 318 sales representatives to 671, and its total physician call list from approximately 33 400 to 44 500 to approximately 70 500 to 94 000 physicians.[19] Through the sales representatives, Purdue used a patient starter coupon program for OxyContin that provided patients with a free limited-time prescription for a 7- to 30-day supply. By 2001, when the program was ended, approximately 34 000 coupons had been redeemed nationally.[19]

The distribution to health care professionals of branded promotional items such as OxyContin fishing hats, stuffed plush toys, and music compact discs ("Get in the Swing With OxyContin") was unprecedented for a schedule II opioid, according to the Drug Enforcement Administration.[19]

Purdue promoted among primary care physicians a more liberal use of opioids, particularly sustained-release opioids. Primary care physicians began to use more of the increasingly popular OxyContin; by 2003, nearly half of all physicians prescribing OxyContin were primary care physicians.[19] Some experts were concerned that primary care physicians were not sufficiently trained in pain management or addiction issues.[23] Primary care physicians, particularly in a managed care environment of time constraints, also had the least amount of time for evaluation and follow-up of patients with complicated chronic pain.

Purdue "aggressively" promoted the use of opioids for use in the "non-malignant pain market."[15(p187)] A much larger market than that for cancer-related pain, the non–cancer-related pain market constituted 86% of the total opioid market in 1999.[17] Purdue's promotion of OxyContin for the treatment of non–cancer-related pain contributed to a nearly tenfold increase in OxyContin prescriptions for this type of pain, from about 670 000 in 1997 to about 6.2 million in 2002, whereas prescriptions for cancer-related pain increased about fourfold during that same period.[19] Although the science and consensus for the use of opioids in the treatment of acute pain or pain associated with cancer are robust, there is still much controversy in medicine about the use of opioids for chronic non–cancer-related pain, where their risks and benefits are much less clear. Prospective, randomized, controlled trials lasting at least 4 weeks that evaluated the use of opioids for chronic, non–cancer-related pain showed statistically significant but small to modest improvement in pain relief, with no consistent improvement in physical functioning.[24–38] A recent review of the use of opioids in chronic back pain concluded that opioids may be efficacious for short-term pain relief, but longer-term efficacy (> 16 weeks) is unclear.[39]

In the long-term use of opioids for chronic non–cancer-related pain, the proven analgesic efficacy must be weighed against the following potential problems and risks: well-known opioid side effects, including respiratory depression, sedation, constipation, and nausea; inconsistent improvement in functioning; opioid-induced hyperalgesia; adverse hormonal and immune effects of long-term opioid treatment; a high incidence of prescription opioid abuse behaviors; and an ill-defined and unclarified risk of iatrogenic addiction.[40]

MISREPRESENTING THE RISK OF ADDICTION

A consistent feature in the promotion and marketing of OxyContin was a systematic effort to minimize the risk of addiction in the use of opioids for the treatment of chronic non–cancer-related pain. One of the most critical issues regarding the use of opioids in the treatment of chronic non–cancer-related pain is the potential of iatrogenic addiction. The lifetime prevalence of addictive disorders has been estimated at 3% to 16% of the general population.[41] However, we lack any large, methodically rigorous prospective study addressing the issue of iatrogenic addiction during long-term opioid use for chronic nonmalignant pain.[42]

In much of its promotional campaign—in literature and audiotapes for physicians, brochures and videotapes for patients, and its "Partners Against Pain" Web site—Purdue claimed that the risk of addiction from OxyContin was extremely small.[43–49]

Purdue trained its sales representatives to carry the message that the risk of addiction was "less than one percent."[50(p99)] The company cited studies by Porter and Jick,[51] who found iatrogenic addiction in only 4 of 11 882 patients using opioids and by Perry and Heidrich,[52] who found no addiction among 10 000 burn patients treated with opioids. Both of these studies, although shedding some light on the risk of addiction for acute pain, do not help establish the risk of iatrogenic addiction when opioids are used daily for a prolonged time in treating chronic pain. There are a number of studies, however, that demonstrate that in the treatment of chronic non–cancer-related pain with opioids, there is a high incidence of prescription drug abuse. Prescription drug abuse in a substantial minority of chronic-pain patients has been demonstrated in studies by Fishbain et al. (3%–18% of patients),[53] Hoffman et al. (23%),[54] Kouyanou et al. (12%),[55] Chabal et al. (34%),[56] Katz et al. (43%),[57] Reid et al. (24%–31%),[58] and Michna et al. (45%).[59] A recent literature review showed that the prevalence of addiction in patients with long-term opioid treatment for chronic non–cancer-related pain varied from 0% to 50%, depending on the criteria used and the subpopulation studied.[60]

Misrepresenting the risk of addiction proved costly for Purdue. On May 10, 2007, Purdue Frederick Company Inc, an affiliate of Purdue Pharma, along with 3 company executives, pled guilty to criminal charges of misbranding OxyContin by claiming that it was less addictive and less subject to abuse and diversion than other opioids, and will pay $634 million in fines.[61]

Although research demonstrated that OxyContin was comparable in efficacy and safety to other available opioids,[11,63] marketing catapulted OxyContin to blockbuster drug status. Sales escalated from $44 million (316 000 prescriptions dispensed) in 1996 to a 2001 and 2002 combined sales of nearly $3 billion (over 14 million prescriptions).[12]

The remarkable commercial success of OxyContin, however, was stained by increasing rates of abuse and addiction. Drug abusers learned how to simply crush the controlled-release tablet and swallow, inhale, or inject the high-potency opioid for an intense morphinelike high.[64] There had been some precedence for the diversion and abuse of controlled-release opioid preparations. Purdue's own MS Contin had been abused in the late 1980s in a fashion similar to how OxyContin was later to be; by 1990, MS Contin had become the most abused prescription opioid in one major metropolitan area.[65] Purdue's own testing in 1995 had demonstrated that 68% of the oxycodone could be extracted from an OxyContin tablet when crushed.[66]

Opioid prescribing has had significant geographical variations. In some areas, such as Maine, West Virginia, eastern Kentucky, southwestern Virginia, and Alabama, from 1998 through 2000, hydrocodone and (non-OxyContin) oxycodone were being prescribed 2.5 to 5.0 times more than the national average. By 2000, these same areas had become high OxyContin-prescribing areas—up to 5 to 6 times higher than the national average in some counties (Table 1).[67] These areas, in which OxyContin was highly available, were the first in the nation to witness increasing OxyContin abuse and diversion, which began surfacing in 1999 and 2000.[23] From 1995 to 2001, the number of patients treated for opioid abuse in Maine increased 460%, and from 1997 to 1999 the state had a 400% increase in the number of chronic hepatitis C cases reported.[68] In eastern Kentucky from 1995 to 2001, there was a 500% increase in the number of patients entering methadone maintenance treatment programs, about 75% of whom were OxyContin dependent (Mac Bell, administrator, Narcotics Treatment Programs, Kentucky Division of Substance Abuse, written communication, March 2002). In West Virginia, the first methadone maintenance treatment program opened in August 2000, largely in response to the increasing number of people with OxyContin dependence. By October 2003, West Virginia had 7 methadone maintenance treatment clinics with 3040 patients in treatment (M. Moore, Office of Behavioral Health Services, Office of Alcoholism and Drug Abuse, West Virginia, written communication, March 16, 2004). In southwestern Virginia, the first methadone maintenance treatment program opened in March 2000, and within 3 years it had 1400 admissions (E. Jennings, Life Center of Galax, Galax, Virginia, written communication, March 12, 2004).

TABLE 1
Distribution of OxyContin, Oxycodone (Excluding OxyContin), and Hydrocodone per 100 000 Population: Virginia, West Virginia, and Kentucky, 2000

With increasing diversion and abuse, opioid-related overdoses escalated. In southwest Virginia, the number of deaths related to opioid prescriptions increased 830%, from 23 in 1997 to 215 in 2003 (William Massello III, MD, assistant chief medical examiner, Office of Chief Medical Examiner, Western District, Virginia Department of Health, written communication, January 12, 2007). The high availability of OxyContin in these 5 regions seemed to be a simple correlate of its abuse, diversion, and addiction.

With the growing availability of OxyContin prescriptions, the once-regional problem began to spread nationally. By 2002, OxyContin accounted for 68% of oxycodone sales.[69] Lifetime nonmedical use of OxyContin increased from 1.9 million to 3.1 million people between 2002 and 2004, and in 2004 there were 615 000 new nonmedical users of OxyContin.[70] By 2004, OxyContin had become the most prevalent prescription opioid abused in the United States.[2]

The increasing OxyContin abuse problem was an integral part of the escalating national prescription opioid abuse problem. Liberalization of the use of opioids, particularly for the treatment of chronic non–cancer-related pain, increased the availability of all opioids as well as their abuse. Nationwide, from 1997 to 2002, there was a 226%, 73%, and 402% increase in fentanyl, morphine, and oxycodone prescribing, respectively

(in grams per 100 000 population). During that same period, the Drug Abuse Warning Network reported that hospital emergency department mentions for fentanyl, morphine, and oxycodone increased 641%, 113%, and 346%, respectively.[71] Among new initiates to illicit drug use in 2005, a total of 2.1 million reported prescription opioids as the first drug they had tried, more than for marijuana and almost equal to the number of new cigarette smokers (2.3 million).[72] Most abusers of prescription opioids get their diverted drugs directly from a doctor's prescription or from the prescriptions of friends and family.[73]

In terms of illicit drug abuse, prescription opioids are now ahead of cocaine and heroin and second only to marijuana.[72] Mortality rates from drug overdose have climbed dramatically; by 2002, unintentional overdose deaths from prescription opioids surpassed those from heroin and cocaine nationwide.[74] Nationally, as well as regionally, the high availability of OxyContin and all prescription opioids was correlated with high rates of abuse and diversion.

THE FOOD AND DRUG ADMINISTRATION

Under the Food, Drug, and Cosmetics Act and implementing regulations, the FDA regulates the advertising and promotion of prescription drugs and is responsible for ensuring that prescription drug advertising and promotion are truthful, balanced, and accurately communicated. There is no distinction in the act between controlled and noncontrolled drugs regarding the oversight of promotional activities. Although regulations require that all promotional materials for prescription drugs be submitted to the FDA for review when the materials are initially disseminated or used, it is generally not required that these materials be approved by the FDA prior to their use. The FDA has a limited number of staff for overseeing the enormous amount of promotional materials. In 2002, for example, 39 FDA staff members were responsible for reviewing roughly 34 000 pieces of promotional materials.[19] This limited staffing significantly diminishes the FDA's ability to ensure that the promotion is truthful, balanced, and accurately communicated.

In 1998, Purdue distributed 15 000 copies of an OxyContin video to physicians without submitting it to the FDA for review, an oversight later acknowledged by Purdue. In 2001, Purdue submitted to the FDA a second version of the video, which the FDA did not review until October 2002—after the General Accounting Office inquired about its content. After its review, the FDA concluded that the video minimized the risks from OxyContin and made unsubstantiated claims regarding its benefits to patients.[19]

When OxyContin entered the market in 1996, the FDA approved its original label, which stated that iatrogenic addiction was "very rare" if opioids were legitimately used in the management of pain. In July 2001, to reflect the available scientific evidence, the label was modified to state that data were not available for establishing the true incidence of addiction in chronic-pain patients. The 2001 labeling also deleted the original statement that the delayed absorption of OxyContin was believed to reduce the abuse liability of the drug.[19] A more thorough review of the available scientific evidence prior to the original labeling might have prevented some of the need for the 2001 label revision.

CONCLUSIONS

OxyContin appears to be as efficacious and safe as other available opioids and as oxycodone taken 4 times daily.[11,63] Its commercial success, fueled by an unprecedented promotion and marketing campaign, was stained by escalating OxyContin abuse and diversion that spread throughout the country.[2,75] The regions of the country that had the earliest and highest availability of prescribed OxyContin had the greatest initial abuse and diversion.[23,62] Nationally, the increasing availability of OxyContin was associated with higher rates of abuse, and it became the most prevalent abused prescription opioid by 2004.[2]

Compared with noncontrolled drugs, controlled drugs, with their potential for abuse and diversion, pose different public health risks when overpromoted and highly prescribed. Several marketing practices appear to be especially questionable.

The extraordinary amount of money spent in promoting a sustained-release opioid was unprecedented. During OxyContin's first 6 years on the market, Purdue spent approximately 6 to 12 times more on promoting it than the company had spent on promoting MS Contin, or than Janssen Pharmaceutical Products LP had spent on Duragesic, one of OxyContin's competitors.[19] Although OxyContin has not been shown to be superior to other available potent opioid preparations,[11,62] by 2001 it had become the most frequently prescribed brand-name opioid in the United States for treating moderate to severe pain.[19] Carefully crafted limits on the marketing and promotion of controlled drugs would help to realign their actual use with the principles of evidence-based medicine.

Physicians' interactions with pharmaceutical sales representatives have been found to influence the prescribing practices of residents and physicians in terms of decreased prescribing of generic drugs, prescribing cost, nonrational prescribing, and rapid prescribing of new drugs.[76] Carefully crafted limits on the promotion of controlled drugs by the pharmaceutical sales force and enhanced FDA oversight of the training and performance of sales representatives would also reduce over- and misprescribing.

Although there are no available data for evaluating the promotional effect of free starter coupons for controlled drugs, it seems likely that the over- and misprescribing of a controlled drug are encouraged by such promotional programs and the public health would be well served by eliminating them.

The use of prescriber profiling data to influence prescribing and improve sales is imbedded in pharmaceutical detailing. Very little data are publicly available for understanding to what extent this marketing practice boosts sales. One market research report indicated that profiling improved profit margins by as much as 3 percentage points and the initial uptake of new drugs by 30%.[77] The use of prescriber profiling data to target high-opioid prescribers—coupled with very lucrative incentives for sales representatives—would seem to fuel increased prescribing by some physicians—perhaps the most liberal prescribers of opioids and, in some cases, the least discriminate. Regulations eliminating this marketing tool might decrease some potential overprescribing of controlled drugs.

The public health would be better protected if the FDA reviewed all advertising and promotional materials as well as associated educational materials—for their truthfulness, accuracy, balance, and scientific validity—*before* dissemination. Such a change would require a considerable increase in FDA support, staffing, and funding from what is currently available. Public monies spent on the front end of the problem could prevent another such tragedy.

The pharmaceutical industry's role and influence in medical education is problematic. From 1996 through July 2002, Purdue funded more than 20 000 pain-related educational programs through direct sponsorship or financial grants,[19] providing a venue that had enormous influence on physicians' prescribing throughout the country. Particularly with controlled drugs, the potential for blurring marketing and education carries a much higher public health risk than with uncontrolled drugs. At least in the area of controlled drugs, with their high potential for abuse and diversion, public health would best be served by severing the pharmaceutical industry's direct role and influence in medical education.

Marketing and promotion by the pharmaceutical industry have considerably amplified the prescription sales and availability of opioids. A number of factors have contributed to the marked growth of opioid abuse in the United States, but one factor is certainly the much increased availability of prescription opioids.[78] The public interest and public health would be better served by a redefinition of acceptable and allowable marketing practices for opioids and other controlled drugs.

Acknowledgments

I thank Michael McNeer, MD, for his thoughtful review of the essay and helpful suggestions.

References

1. "OxyContin Marketing Plan, 2002." Purdue Pharma, Stamford, CN, 2002
2. Cicero T, Inciardi J, Munoz A. Trends in abuse of OxyContin and other opioid analgesics in the United States: 2002–2004. J Pain 2005;6:662–672 [PubMed]
3. Oxycodone and OxyContin. Med Lett Drugs Ther 2001;43:80–81 [PubMed]
4. Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in chronic back pain. Clin J Pain 1999;15:179–183 [PubMed]
5. Kaplan R, Parris WC, Citron ML, et al. Comparison of controlled-release and immediate-release oxycodone in cancer pain. J Clin Oncol 1998;16:3230–3237 [PubMed]
6. Staumbaugh JE, Reder RF, Stambaugh MD, et al. Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate-release oral oxycodone in cancer pain patients. J Clin Pharmacol 2001;41:500–506 [PubMed]
7. Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. Pain 1997;73:37–45 [PubMed]
8. Mucci-LoRusso P, Berman BS, Silberstein PT, et al. Controlled-release oxycodone compared with controlled-release morphine in treatment of cancer pain: a randomized, double-blind, parallel-group study. Eur J Pain 1998;2:239–249 [PubMed]
9. Bruera E, Belzile M, Pituskin E, et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. J Clin Oncol 1998;16:3222–3229 [PubMed]
10. "New Drug Application for OxyContin." Purdue Pharma, Stamford, CN December 1995.
11. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain. J Pain Symptom Manage 2003;26(5):1026–1048 [PubMed]
12. "OxyContin Marketing Plan, 1996." Purdue Pharma, Stamford, CN.
13. "OxyContin Marketing Plan, 1997." Purdue Pharma, Stamford, CN.
14. "OxyContin Marketing Plan, 1998." Purdue Pharma, Stamford, CN.
15. "OxyContin Marketing Plan, 1999." Purdue Pharma, Stamford, CN.
16. "OxyContin Marketing Plan, 1996." Purdue Pharma, Stamford, CN.
17. "OxyContin Marketing Plan, 2001." Purdue Pharma, Stamford, CN.
18. "OxyContin: balancing risks and benefits," in *Hearing of the Committee on Health, Education, Labor, and Pensions, United States Senate*, February 12, 2002, p 87 (testimony of Paul Goldenheim, Purdue Pharma)
19. Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem. Washington, DC: General Accounting Office; December 2003. Publication GAO-04-110
20. Orlowski JP, Wateska L. The effect of pharmaceutical firm enticements on physician prescribing patterns. There's no such thing as a free lunch. Chest 1992;102:270–273 [PubMed]
21. Stolberg SG, Gerth J. High-tech stealth being used to sway doctor prescriptions. New York Times November 16, 2000. Available at: http://query.nytimes.com/gst/fullpage.html?res=9502EEDF153BF935A25752C1A9669C8B63&sec=&spon=&pagewanted=1. Accessed September 11, 2008 [PubMed]
22. Adams C. Painkiller's sales far exceeded levels anticipated by maker. Wall Street Journal May 16, 2002
23. Tough P. The alchemy of OxyContin: from pain relief to drug addiction. New York Times Magazine July 29, 2001:37
24. Moulin DE, Iezzi A, Amireh R, et al. Randomized trial of oral morphine for chronic non-cancer pain. Lancet 1996;346:143–147 [PubMed]
25. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic pain. Neurology 1998;50:1837–1841 [PubMed]
26. Caldwell JR, Rapoport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. J Pain Symptom Manage 2002;23:178–291 [PubMed]
27. Gimbel J, Richards P, Portenoy R. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. Neurology 2003;60:927–934 [PubMed]

28. Peloso P, Bellamy N, Bensen W, et al. Double blind randomized placebo controlled trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. J Rheumatol 2000;27:764–771 [PubMed]
29. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock controlled-release oxycodone therapy for osteoarthritis-related pain. Arch Intern Med 2000;160:853–860 [PubMed]
30. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal anti-inflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol 1999;26:862–869 [PubMed]
31. Rowbotham MD, Twilling LO, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med 2003;348:1223–1232 [PubMed]
32. Kjaersgaard-Andersen P, Nafei A, Skov O, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip: a randomized, double-blind multicentre study. Pain 1990;43:309–318 [PubMed]
33. Raja SN, Haythornthwaite JA, Pappagallo M, et al. A placebo-controlled trial comparing the analgesic and cognitive effects of opioids and tricyclic antidepressants in postherpetic neuralgia. Neurology 2002;59:1015–1021 [PubMed]
34. Huse E, Larbig W, Flor H, et al. The effect of opioids on phantom limb pain and cortical reorganization. Pain 2001;90:47–55 [PubMed]
35. Moran C. MS continuous tablets and pain control in severe rheumatoid arthritis. Br J Clin Res 1991;2:1–12
36. Jamison RN, Raymond SA, Slawsby EA, et al. Opioid therapy for chronic noncancer back pain: a randomized prospective study. Spine 1998;23:2591–2600 [PubMed]
37. Arkinstall W, Sandler A, Groghnour B, et al. Efficacy of controlled-release codeine in chronic non-malignant pain: a randomized placebo-controlled trial. Pain 1995;62:168–178 [PubMed]
38. Sheather-Reid RB, Cohen ML. Efficacy of analgesics in chronic pain: a series of N-of-1 studies. J Pain Symptom Manage 1998;15:244–252 [PubMed]
39. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. Ann Intern Med 2007;146:116–127 [PubMed]
40. Ballantyne JC. Opioids for chronic nonterminal pain. South Med J 2006;99:1245–1255 [PubMed]
41. Regier DA, Myers JK, Kramer M, et al. The NIMH epidemiological catchment area program. Historical context, major objectives, and study population characteristics. Arch Gen Psychiatry 1984;41:934–941 [PubMed]
42. Katz N. Opioids: after thousands of years, still getting to know you. Clin J Pain 2007;23:303–306 [PubMed]
43. Irick N, Lipman A, Gitlin M. *Overcoming Barriers to Effective Pain Management* [audiotape]. Rochester, NY: Solutions Unlimited; March 2000
44. Carr B, Kulich R, Sukiennik A, et al. *The Impact of Chronic Pain—An Interdisciplinary Perspective.* Continuing Medical Education program. New York, NY: Power-Pak Communications; 2000:925 Program 424-000-99-010-H01
45. Lipman A, Jackson K., II *Use of Opioids in Chronic Noncancer Pain.* Continuing Medical Education program. New York, NY: Power-Pak Communications; April 2000:6
46. *How You Can Be a Partner Against Pain and Gain Control Over Your Own Pain* [patient brochure]. Stamford, CN: Purdue Pharma; 1998
47. "Partners Against Pain" Web site, under "Professional Education" menu and "Opioids and back pain: the last taboo"—2000. Available at: http://www.partnersagainstpain.com/html/proofed/pmc/pc_pmc6.htm. Accessed March 19, 2001.
48. *Pain Management* [CD and slide instructional program for physicians]. Stamford, CN: Purdue Pharma; 2002
49. *Dispelling the Myths About Opioids* [brochure for physicians]. Stamford, CN: Purdue Pharma; 1998
50. Meier B. Pain Killer Emmaus, PA: Rodale Press; 2003:99
51. Porter J, Jick H. Addiction rare in patients treated with narcotics. N Engl J Med 1980;302:123. [PubMed]
52. Perry S, Heidrich G. Management of pain during debridement: a survey of US burn units. Pain 1982;13:267–280 [PubMed]

53. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. Clin J Pain 1992;8:77–85 [PubMed]
54. Hoffmann NG, Olofsson S, Salen B, Wickstrom L. Prevalence of abuse and dependence in chronic pain patients. Int J Addict 1995;30:919–927 [PubMed]
55. Kouyanou K, Pither CE, Wessely S. Medication misuse, abuse, and chronic dependence in chronic pain patients. J Psychosom Res 1997;43:497–504 [PubMed]
56. Chabal C, Erjavec MK, Jacobson L, et al. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. Clin J Pain 13;150–155 [PubMed]
57. Katz NP, Sherburne S, Beach M, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg 2003;97:1097–1102 [PubMed]
58. Reid M, Engles-Horton L, Weber M, et al. Use of opioid medications for chronic non-cancer pain. J Gen Intern Med 2002;17:173–179 [PMC free article] [PubMed]
59. Michna E, Jamison RN, Pham LD, et al. Urine toxicology screening among chronic pain patients on opioid therapy: frequency and predictability of abnormal findings. Clin J Pain 2007;23:173–179 [PubMed]
60. Hojsted J, Sjogren P. Addiction to opioids in chronic pain patients: a literature review. Eur J Pain 2007;11:490–518 [PubMed]
61. United States Attorney's Office Western District of Virginia [news release]. Available at: http://www.dodig.osd.mil/IGInformation/IGInformationReleases/prudue_frederick_1.pdf. Accessed September 11, 2008
62. *United States of America v The Purdue Frederick Company Inc et al.*, (WD Va, May 10, 2007), Case 1:07CR00029.
63. Rischitelli DG, Karbowicz SH. Safety and efficacy of controlled-release oxycodone: a systematic literature review. Pharmacotherapy 2002;22:898–904 [PubMed]
64. Drug Enforcement Administration, Office of Diversion Control Action plan to prevent the diversion and abuse of OxyContin. Available at: http://www.deadiversion.usdoj.gov/drugs_concern/oxycodone/abuse_oxy.htm. Accessed March 12, 2008
65. Crews JC, Denson DD. Recovery of morphine from a controlled-release preparation: a source of opioid abuse. Cancer 1990;66:2642–2644 [PubMed]
66. "New Drug Application to FDA for OxyContin, Pharmacology Review: 'Abuse Liability of Oxycodone.' " Purdue Pharma, Stamford, CN, 1995
67. States of Alabama, Maine, Kentucky, Virginia, and West Virginia Drug Profile by County—OxyContin, Oxycodone (Excluding OxyContin), and Hydrocodone—2000. Washington, DC: Office of Diversion Control, Drug Enforcement Administration; 2002
68. OxyContin Abuse: Maine's Newest Epidemic. Augusta: Maine Office of Substance Abuse; January 2002
69. Paulozzi LJ. Opioid analgesic involvement in drug abuse deaths in American metropolitan areas. Am J Public Health 2006;96:1755–1757 [PMC free article] [PubMed]
70. Substance Abuse and Mental Health Services Administration. National Survey on Drug Use and Health. Available at: http://www.oas.samhsa.gov/NSDUH/2k4nsduh/2k4Results/2k4Results.pdf. Accessed March 12, 2008
71. Gilson AM, Ryan KM, Joranson DE, et al. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. J Pain Symptom Manage 2004;28:176–188 [PubMed]
72. Substance Abuse and Mental Health Services Administration Results from the 2005 National Survey on Drug Use and Health: national findings. Available at: http://www.oas.samhsa.gov/nsduh/2k5nsduh/2k5Results.pdf. Accessed March 12, 2008
73. Substance Abuse and Mental Health Services Administration Results from the 2006 National Survey on Drug Use and Health. Available at: http://www.oas.samhsa.gov/nsduh/2k6nsduh/2k6Results.pdf. Accessed March 12, 2008
74. Paulozzi LJ, Budnitz DS, Yongli X. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 2006;15:618–627 [PubMed]
75. Pulse Check: Trends in Drub Abuse. Washington, DC: Office of National Drug Control Policy, Executive Office of the President; November 2002
76. Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? JAMA 2000;283:373–380 [PubMed]
77. Grande D. Prescribing profiling: time to call it quits. Ann Intern Med 2007;146:751–752 [PubMed]

78. Compton W, Volkow N. Major increases in opioid analgesic abuse in the United States: concerns and strategies. Drug Alcohol Depend 2006;81:103–107 [PubMed]

Formats:

- Article

  |

- PubReader

  |

- ePub (beta)

  |

- PDF (539K)

  |

- Citation

Share

- Facebook
- Twitter
- Google+

Save items

View more options

Similar articles in PubMed

- The danger of imperfect regulation: OxyContin use in the United States and Canada.[Int J Risk Saf Med. 2011]
- OxyContin abuse and diversion and efforts to address the problem: highlights of a government report.[J Pain Palliat Care Pharmacoth...]
- Impact of abuse-deterrent OxyContin on prescription opioid utilization.[Pharmacoepidemiol Drug Saf. 2015]
- Controlled-release oxycodone hydrochloride (OxyContin).[Clin Nurse Spec. 2001]

- Risk evaluation and mitigation strategies for drugs with abuse liability: public interest, special interest, conflicts of interest, and the industry perspective.[Ann N Y Acad Sci. 2008]

See reviews...See all...

Cited by other articles in PMC

- Nonvitamin, Nonmineral Dietary Supplement Use among Adults with Fibromyalgia: United States, 2007–2012[Evidence-based Complementary a...]
- The opioid overdose epidemic: opportunities for pharmacists[Substance Abuse and Rehabilita...]
- Methodological quality of systematic reviews referenced in clinical practice guidelines for the treatment of opioid use disorder[PLoS ONE. 2017]
- Shifting blame: Buprenorphine prescribers, addiction treatment, and prescription monitoring in middle-class America[Transcultural psychiatry. 2016]
- Buprenorphine and methadone treatment for opioid dependence by income, ethnicity and race of neighborhoods in New York City[Drug and alcohol dependence. 2...]

See all...

Links

- Compound
- MedGen
- PubMed
- Substance
- Taxonomy

Recent Activity

Clear Turn Off

- The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Trag...

  The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy

  American Journal of Public Health. 2009 February; 99(2)221

- The danger of imperfect regulation: OxyContin use in the United States and Canad...

  The danger of imperfect regulation: OxyContin use in the United States and Canada.

  Int J Risk Saf Med. 2011;23(4):233-40. doi: 10.3233/JRS-2011-0539.

  PubMed

- Preventive Measures to Eliminate Asbestos-Related Diseases in Singapore

  Preventive Measures to Eliminate Asbestos-Related Diseases in Singapore

  Safety and Health at Work. 2011 Sep; 2(3)201

See more...

- The effects of pharmaceutical firm enticements on physician prescribing patterns. There's no such thing as a free lunch.[Chest. 1992]

- High-tech stealth being used to sway doctor prescriptions.[N Y Times Web. 2000]

- Randomised trial of oral morphine for chronic non-cancer pain.[Lancet. 1996]
- Efficacy of analgesics in chronic pain: a series of N-of-1 studies.[J Pain Symptom Manage. 1998]
- Review Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction.[Ann Intern Med. 2007]

- Review Opioids for chronic nonterminal pain.[South Med J. 2006]

- The NIMH Epidemiologic Catchment Area program. Historical context, major objectives, and study population characteristics.[Arch Gen Psychiatry. 1984]
- Review Opioids: after thousands of years, still getting to know you.[Clin J Pain. 2007]

- Addiction rare in patients treated with narcotics.[N Engl J Med. 1980]
- Management of pain during debridement: a survey of U.S. burn units.[Pain. 1982]
- Review Drug abuse, dependence, and addiction in chronic pain patients.[Clin J Pain. 1992]
- Prevalence of abuse and dependency in chronic pain patients.[Int J Addict. 1995]
- Medication misuse, abuse and dependence in chronic pain patients.[J Psychosom Res. 1997]
- Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors.[Clin J Pain. 1997]

See more ...

- Review Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review.[J Pain Symptom Manage. 2003]
- Review Safety and efficacy of controlled-release oxycodone: a systematic literature review.[Pharmacotherapy. 2002]

- Recovery of morphine from a controlled-release preparation. A source of opioid abuse.[Cancer. 1990]

- Opioid analgesic involvement in drug abuse deaths in American metropolitan areas.[Am J Public Health. 2006]
- Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2002-2004.[J Pain. 2005]

- A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997-2002.[J Pain Symptom Manage. 2004]

- Increasing deaths from opioid analgesics in the United States.[Pharmacoepidemiol Drug Saf. 2006]

- Review Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review.[J Pain Symptom Manage. 2003]
- Review Safety and efficacy of controlled-release oxycodone: a systematic literature review.[Pharmacotherapy. 2002]

- Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2002-2004.[J Pain. 2005]

- Review Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review.[J Pain Symptom Manage. 2003]
- Review Safety and efficacy of controlled-release oxycodone: a systematic literature review.[Pharmacotherapy. 2002]

- Physicians and the pharmaceutical industry: is a gift ever just a gift?[JAMA. 2000]

- Prescriber profiling: time to call it quits.[Ann Intern Med. 2007]

- Review Major increases in opioid analgesic abuse in the United States: concerns and strategies.[Drug Alcohol Depend. 2006]

Support Center Support Center

EXHIBIT C

Industry Payments to Physicians for Opioid Products, 2013–2015

Scott E. Hadland, MD, MPH, MS, Maxwell S. Krieger, BS, and Brandon D. L. Marshall, PhD

Objectives. To identify payments that involved opioid products from the pharmaceutical industry to physicians.

Methods. We used the Open Payments program database from the Centers for Medicare and Medicaid Services to identify payments involving an opioid to physicians between August 2013 and December 2015. We used medians, interquartile ranges, and ranges as a result of heavily skewed distributions to examine payments according to opioid product, abuse-deterrent formulation, nature of payment, state, and physician specialty.

Results. During the study, 375 266 nonresearch opioid-related payments were made to 68 177 physicians, totaling $46 158 388. The top 1% of physicians received 82.5% of total payments in dollars. Abuse-deterrent formulations constituted 20.3% of total payments, and buprenorphine marketed for addiction treatment constituted 9.9%. Most payments were for speaking fees or honoraria (63.2% of all dollars), whereas food and beverage payments were the most frequent (93.9% of all payments). Physicians specializing in anesthesiology received the most in total annual payments (median = $50; interquartile range = $16–$151).

Conclusions. Approximately 1 in 12 US physicians received a payment involving an opioid during the 29-month study. These findings should prompt an examination of industry influences on opioid prescribing. (*Am J Public Health.* 2017;107:1493–1495. doi: 10.2105/AJPH.2017.303982)

The nonmedical use of opioids and overdose mortality have reached unprecedented levels in the United States.[1] To respond to concerns about overprescribing of opioids, the Centers for Disease Control and Prevention recently released chronic pain management guidelines that call on physicians to consider nonopioid pain medications as an alternative to opioids.[2] Additionally, some physicians and pharmaceutical industry representatives have suggested that abuse-deterrent formulations—newly marketed brand-name opioids with pill properties that render misuse more difficult—offer a safer option for prescribers.[3,4]

Under the recently implemented Physician Payments Sunshine Act, drug companies are now required to report all transfers of value ("payments") to US physicians.[5] Research suggests that pharmaceutical company payments promote increased prescribing for marketed brand-name medications, even when payments are of low monetary value (e.g., industry-sponsored meals).[6] To date, industry payments to physicians involving opioids have not been studied and deserve further examination because they may impede national efforts to reduce overprescribing.

It is currently unclear which opioids are most heavily marketed, to whom, and in exchange for which physician activities. The extent to which abuse-deterrent formulations and nonopioid alternatives are marketed is also poorly understood. For the first time, exhaustive data on payments are now available through the Open Payments program database implemented under the Physician Payments Sunshine Act.[5,7] We used this novel data set to characterize industry payments to physicians related to opioid marketing.

METHODS

We extracted all payments between August 1, 2013 (when mandated reporting began), and December 31, 2015, that listed a US Food and Drug Administration (FDA)–approved opioid product. We included buprenorphine but examined buprenorphine and buprenorphine/naloxone marketed for addiction treatment separately from the buprenorphine transdermal patch marketed for pain control. We excluded remifentanil (which is marketed exclusively for anesthesia) and 2 fentanyl products (1 marketed exclusively for anesthesia, and 1 marketed exclusively for in-hospital pain).

We also identified payments involving FDA-recognized abuse-deterrent opioid formulations.[8] For comparison with a nonopioid class of pain medications, we quantified payments for all actively marketed nonsteroidal anti-inflammatory drugs (NSAIDs) in the database. We chose NSAIDs for this comparison because unlike other medication classes used for pain that have additional indications (e.g., medications marketed not only for pain but also for depression or neuralgia), NSAIDs are almost exclusively used for pain control.

We limited the current analysis to nonresearch payments to physicians; we excluded research payments, which are made in

ABOUT THE AUTHORS

Scott E. Hadland is with Boston Medical Center and Boston University School of Medicine, Boston, MA. Maxwell S. Krieger and Brandon D. L. Marshall are with Brown University School of Public Health, Providence, RI.

Correspondence should be sent to Scott E. Hadland, MD, MPH, MS, 88 E Newton St, Vose Hall, Room 322, Boston, MA 02118 (e-mail: scott.hadland@bmc.org). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This article was accepted June 14, 2017.

doi: 10.2105/AJPH.2017.303982

association with established research protocols, do not explicitly target prescribing behaviors, and may be provided to physicians not actively practicing medicine. We summarized payments in terms of total dollars and number of payments made and identified changes from 2014 to 2015 (the 2 years for which all 12 months of data were available). We used medians, interquartile ranges (IQRs), and ranges as a result of heavily skewed distributions to examine payments according to opioid product, abuse-deterrent formulation, nature of payment (i.e., physician activity leading to the payment), state, and physician specialty. We also assessed payments to physicians receiving the top 1% of payments for opioids. We used Stata version 13.1 (StataCorp LP, College Station, TX) for analyses.

RESULTS

Over the study period, 375 266 nonresearch payments involving a marketed opioid were made to 68 177 physicians, totaling $46 158 388. Total payments increased from $18 958 125 in 2014 to $20 996 858 in 2015, an increase of 10.7%. The number of payments increased from 145 715 in 2014 to 184 237 in 2015, an increase of 26.4%.

The 5 opioid products constituting the greatest proportion of payments were fentanyl ($21 240 794; 46.0% of total dollars), hydrocodone ($7 123 421; 15.4%), buprenorphine transdermal patch ($5 141 808; 11.1%), oxycodone ($4 487 978; 9.7%), and tapentadol ($4 296 130; 9.3%). Overall, payments for FDA-approved abuse-deterrent formulations totaled $9 352 959 (20.3%), and payments for buprenorphine or buprenorphine/naloxone marketed for addiction treatment totaled $4 561 729 (9.9%). By comparison, payments for NSAIDs amounted to $13 758 385 (not included in previous totals).

Speaking fees or honoraria constituted the largest proportion of payments in dollars, whereas payments involving food and beverage were the most common (Table 1). Payments varied widely according to US state (Figure A, available as a supplement to the online version of this article at http://www.ajph.org). The median paid per physician annually was $15 (IQR = $7–$42; maximum = $1 539 471), with physicians receiving a median of 1 payment annually (IQR = 1–2; maximum = 157). Payments were positively skewed, with the top 1% of physicians (n = 681) receiving $2639 or more annually (Table A, available as a supplement to the online version of this article at http://www.ajph.org). These physicians collectively received $38 073 796 (82.5% of total payments) during the study period.

TABLE 1—Characteristics of Payments Involving Opioid Products to Physicians: Open Payments Program Database, United States, August 1, 2013–December 31, 2015

Nature of Payment	Total Payment Amount, $ (%)	Median Payment, $ (IQR)	No. of Payments (%)
Speaking fees or honoraria	29 190 854 (63.2)	2 010 (1 000–3 750)	9 161 (2.4)
Food and beverages	7 872 581 (17.1)	14 (11–18)	352 298 (93.9)
Consulting fees	5 886 461 (12.8)	1 000 (500–2 500)	2 145 (0.6)
Travel and lodging	2 904 940 (6.3)	537 (100–1 131)	4 048 (1.1)
Education	222 869 (0.5)	14 (5–25)	7 422 (2.0)
Other[a]	80 683 (0.2)	100 (14–500)	192 (0.1)

Note. IQR = interquartile ranges.
[a]Includes gifts, entertainment, and space rental or facility fees.

Physicians specializing in anesthesiology received the most in total annual payments (median = $50; IQR = $16–$151; n = 4339), followed by physical medicine and rehabilitation (median = $48; IQR = $14–$145; n = 3502) and pain medicine (median = $43; IQR = $12–$125; n = 3090). Physicians specializing in family medicine received the largest total number of payments (n = 20 592).

DISCUSSION

According to the Association of American Medical Colleges, there were 829 962 active physicians in the United States at the beginning of the study period in 2013[9]; thus, our results suggest that 1 in 12 physicians received an industry payment involving an opioid during the 29-month study period. Although half of all the annual payments were $15 or less, even small payments (including meals) are associated with increased prescribing of marketed products.[6] FDA-approved abuse-deterrent formulations, which have properties expected to render misuse less likely, constituted only one fifth of the total payments, suggesting that such medications may not be as heavily marketed as other opioids are. Additionally, despite Centers for Disease Control and Prevention recommendations to consider use of nonopioid medications for pain, NSAIDs, a prominent family of nonopioid pain medications, were not as heavily marketed as opioids were.[2]

Fentanyl was the most common opioid involved in payments to physicians. National data implicate fentanyl in a rapidly increasing number of overdose deaths, although most are caused by illicitly manufactured fentanyl.[10] Further studies should clarify the extent to which industry payments contribute to prescribing patterns and overdose rates across geographic regions, particularly given the heterogeneity we observed in payments among states. Although payment amounts in dollar terms were greatest to physicians specializing in anesthesiology, physical medicine and rehabilitation, and pain medicine—specialists with expertise in pain management—family medicine physicians received the largest number of payments, indicating extensive marketing of opioid products to primary care physicians. Because there were 108 917 active family physicians in the United States in 2013,[9] our data highlight that nearly 1 in 5 received an opioid-related payment.

A limitation of this study was the absence of further details about industry-physician interactions; some payments may have supported education on appropriate prescribing behaviors.[11] One tenth of the payments involved buprenorphine marketed for addiction treatment, which may have resulted in improved education on addiction care. Risk Evaluation and Mitigation Strategies programs imposed by the FDA require education on extended-release/long-acting

opioids and on transmucosal fentanyl products, and some industry payments to physicians may have been related to this regulation. Another limitation was that some abuse-deterrent formulations were approved partway through the study period; in future years, such medications might be associated with a greater portion of industry payments.

PUBLIC HEALTH IMPLICATIONS

To our knowledge, this was the first large-scale examination of industry payments involving opioids. Financial transfers were substantial and widespread and may be increasing in number and value. Although opioid prescribing declined nationally during the study period,[12] these results should prompt an examination of industry influences on prescribing amid an ongoing opioid crisis. Further research should examine whether payments are related to opioid misuse and overdose, and policymakers might consider whether caps should be imposed on certain payments. AJPH

CONTRIBUTORS

S. E. Hadland and B. D. L. Marshall designed the study and wrote the protocol. S. E. Hadland conducted the literature review and wrote the first draft of the article. M. S. Krieger undertook data management and statistical analyses with additional input from S. E. Hadland and B. D. L. Marshall. All authors contributed to and approved the final article.

ACKNOWLEDGMENTS

S. E. Hadland is supported by the National Institutes of Health/National Institute on Drug Abuse (Loan Repayment Program Award L40 DA042434). B. D. L. Marshall is supported by the Henry Merrit Wriston Fellowship at Brown University.

We would like to thank Jesse Yedinak, MPA, for her research and administrative assistance and David Fiellin, MD, and Jason Vassy, MD, MPH, SM, for their review of the article.

HUMAN PARTICIPANT PROTECTION

The study was considered exempt by the Brown University institutional review board.

REFERENCES

1. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths - United States, 2000–2014. *MMWR Morb Mortal Wkly Rep.* 2016; 64(50-51):1378–1382.

2. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain–United States, 2016. *JAMA.* 2016;315(15):1624–1645.

3. Webster LR, Markman J, Cone EJ, Niebler G. Current and future development of extended-release, abuse-deterrent opioid formulations in the United States. *Postgrad Med.* 2017;129(1):102–110.

4. Alexander L, Mannion RO, Weingarten B, Fanelli RJ, Stiles GL. Development and impact of prescription opioid abuse deterrent formulation technologies. *Drug Alcohol Depend.* 2014;138:1–6.

5. Agrawal S, Brown D. The Physician Payments Sunshine Act — two years of the open payments program. *N Engl J Med.* 2016;374(10):906–909.

6. DeJong C, Aguilar T, Tseng C-W, Lin GA, Boscardin WJ, Dudley RA. Pharmaceutical industry-sponsored meals and physician prescribing patterns for Medicare beneficiaries. *JAMA Intern Med.* 2016;176(8):1114–1122.

7. Centers for Medicare & Medicaid Services. Open Payments, 2016. Available at: https://www.cms.gov/openpayments. Accessed February 12, 2017.

8. US Food and Drug Administration. FDA facts: abuse-deterrent opioid medications. April 2017. Available at: http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm514939.htm. Accessed July 3, 2017.

9. Association of American Medical Colleges. *2014 Physician Specialty Data Book.* November 2014. Available at: https://members.aamc.org/eweb/upload/PhysicianSpecialtyDatabook2014.pdf. Accessed February 12, 2017.

10. Gladden RM, Martinez P, Seth P. Fentanyl law enforcement submissions and increases in synthetic opioid–involved overdose deaths — 27 states, 2013–2014. *MMWR Morb Mortal Wkly Rep.* 2016;65(33):837–843.

11. Sismondo S. Key opinion leaders and the corruption of medical knowledge: what the Sunshine Act will and won't cast light on. *J Law Med Ethics.* 2013;41(3):635–643.

12. Goodnough A, Tavernise S. Opioid prescriptions drop for first time in two decades. *New York Times.* May 20, 2016:A1.

EXHIBIT D

DOW JONES, A NEWS CORP COMPANY

DJIA 25024.77 0.45% ▲ Nasdaq 7096.30 -0.28% ▼ U.S. 10 Yr -10/32 Yield 2.840% ▼ Crude Oil 61.84 -2.45% ▼ Euro 1.22

THE WALL STREET JOURNAL.

U.S.

A Pain-Drug Champion Has Second Thoughts

By Thomas Catan and Evan Perez

Updated Dec. 17, 2012 11:36 a.m. ET

It has been his life's work. Now, Russell Portenoy appears to be having second thoughts.

Two decades ago, the prominent New York pain-care specialist drove a movement to help people with chronic pain. He campaigned to rehabilitate a group of painkillers derived from the opium poppy that were long shunned by physicians because of their addictiveness.

Dr. Portenoy's message was wildly successful. Today, drugs containing opioids like Vicodin, OxyContin and Percocet are among the most widely prescribed pharmaceuticals in America.

Opioids are also behind the country's deadliest drug epidemic. More than 16,500 people die of overdoses annually, more than all illegal drugs combined.

Now, Dr. Portenoy and other pain doctors who promoted the drugs say they erred by overstating the drugs' benefits and glossing over risks. "Did I teach about pain management, specifically about opioid therapy, in a way that reflects misinformation? Well, against the standards of 2012, I guess I did," Dr. Portenoy said in an interview with The Wall Street Journal. "We didn't know then what we know now."

Recent research suggests a significantly higher risk of addiction than previously thought, and questions whether opioids are effective against long-term chronic pain.

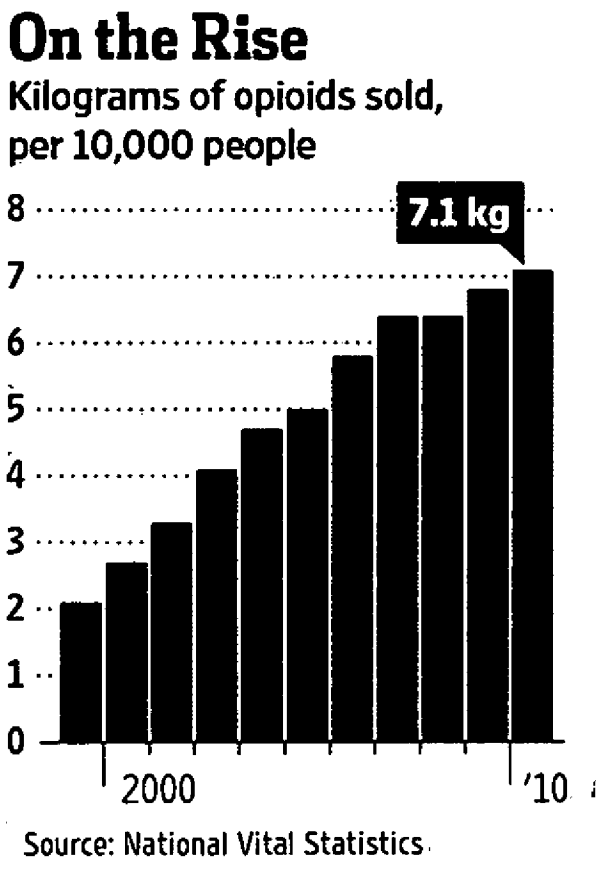
The change of heart among former champions of opioid use has happened quietly, largely beyond the notice of many doctors. New York psychiatrist Joseph Carmody said he was "shocked" after attending a recent lecture outlining the latest findings on opioid risk.

"It goes in the face of everything you've learned," he said. "You saw other doctors come around to it and saying, 'Oh my God, what are we doing?'"

Because doctors feared they were dangerous and addictive, opioids were long reserved mainly for cancer patients. But Dr. Portenoy argued that they could be also safely be taken for months or years by people suffering from chronic pain. Among the assertions he and his followers made in the 1990s: Less than 1% of opioid users became addicted, the drugs were easy to discontinue and overdoses were extremely rare in pain patients.

Many of those experts now say those claims were weren't based on sound scientific evidence. "I gave innumerable lectures in the late 1980s and '90s about addiction that weren't true," Dr. Portenoy said in a 2010 videotaped interview with a fellow doctor. The Journal reviewed the conversation, much of which is previously unpublished.

In it, Dr. Portenoy said it was "quite scary" to think how the growth in opioid prescribing driven by people like him had contributed to soaring rates of addiction and overdose deaths. "Clearly, if I had an inkling of what I know now then, I wouldn't have spoken in the way that I spoke. It was clearly the wrong thing to do," Dr. Portenoy said in the recording.



Speaking to the Journal in September, Dr. Portenoy tempered that statement with cautions about overturning what he sees as the positive change he achieved. He cited his 82-year-old mother, who has taken hydrocodone to control arthritis for 15 years. "If you insist on regulation, then you're consigning my mother and many millions of people like my mother to live in chronic pain," he said.

Virtually no one wants to return to a time when doctors were reluctant to use opioids even for cancer patients. All sides also agree that there is a group of people who do well on opioids long-term, taming their pain while avoiding addiction or excessive sedation, although there is no research on how large this group is or how to identify them before they begin a treatment. There is also widespread agreement that they can be used, with caution, for acute pain, such as after an operation.

But some specialists now question whether the drugs should be prescribed so freely for

months or years to people with chronic pain that isn't related to cancer, as Dr. Portenoy proposed 25 years ago. "People lost sight of the fact that these are dangerous drugs that are highly addictive," said Jane Ballantyne, a pain specialist at the University of Washington. She once agreed with Dr. Portenoy and proponents of broad opioid use but now believes they need to be used more selectively.

Opium-derived painkillers have been around for thousands of years. Early in the 20th century, heroin was sold as a cough suppressant. Heroin addiction in the U.S. skyrocketed. Congress banned the drug in 1924 and doctors became deeply wary about using opioids.

Dr. Portenoy set out to change that. As a young doctor at Memorial Sloan-Kettering hospital in New York, he noticed that opioids were effective in cancer patients with terrible pain.

In 1986, at the age of 31, he co-wrote a seminal paper arguing that opioids could also be used in the much larger group of people without cancer who suffered chronic pain. The paper was based on just 38 cases and included several caveats. Nevertheless, it opened the door to much broader prescribing of the drugs for more common complaints such as nerve or back pain.

Charming and articulate, he became a sought-after public speaker. He argued that opioids are a "gift from nature" that were being forsaken because of "opiophobia" among doctors. "We had to destigmatize these drugs," said Dr. Portenoy.

He rose to chairman of pain medicine and palliative care at Beth Israel Medical Center in New York. His small office is studded with awards and evidence of his offbeat sense of humor. He prominently displays a magazine mock-up that jokingly dubs him "The King of Pain."

At medical conferences, his confident, knowing manner helped smooth the way for his message. Before an audience of government regulators, he once joked that he might tell a patient at low risk of abuse: "Here, [have] six months of drugs. See you later," he said, according to a Food and Drug Administration transcript. Amid laughter, he added, "It's just hyperbole. I don't actually do that."

Steven Passik, a psychologist who once worked closely with Dr. Portenoy and describes him as his mentor, says their message wasn't based on scientific evidence so much as a zeal to improve patients' lives. "It had all the makings of a religious movement at the time," he says. "It had that kind of a spirit to it."

Drug companies took notice. In 1996, Purdue Pharma LP released OxyContin, a form of oxycodone in a patented, time-release form, and rivals followed suit. Today, sales of opioid painkillers total more than $9 billion a year, according to IMS Health, which tracks sales for drug companies.

In 2007, Purdue Pharma and three executives pleaded guilty to "misbranding" of the drug as less addictive and less subject to abuse than other pain medicines and paid $635 million in fines.

Purdue Pharma says it has worked to discourage abuse of its drugs, adding that OxyContin is safe and effective when used properly.

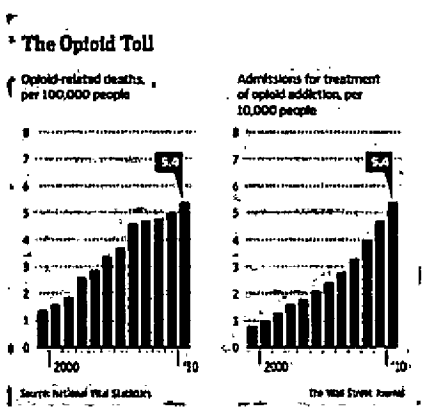
In the late 1990s, groups such as the American Pain Foundation, of which Dr. Portenoy was a director, urged tackling what they called an epidemic of untreated pain. The American Pain Society, of which he was president, campaigned to make pain what it called the "fifth vital sign" that doctors should monitor, alongside blood pressure, temperature, heartbeat and breathing.

Dr. Portenoy helped write a landmark 1996 consensus statement by two professional pain societies that said there was little risk of addiction or overdose among pain patients. In lectures he cited the statistic that less than 1% of opioid users became addicted.

Today, even proponents of opioid use say that figure was wrong. "It's obviously crazy to think that only 1% of the population is at risk for opioid addiction," said Lynn Webster, president-elect of the American Academy of Pain Medicine, one of the publishers of the 1996 statement. "It's just not true."

The figure came from a single-paragraph report in the New England Journal of Medicine in 1980 describing hospitalized patients briefly given opioids. Dr. Portenoy now says he shouldn't have used the information in lectures because it wasn't relevant for patients with chronic noncancer pain.

For such a widely used therapy, there is relatively little scientific evidence that opioid drugs are safe and effective for long-term use. "Data about the effectiveness of opioids does not exist," Dr. Portenoy said in his recent Journal interview. To get a painkiller approved, companies must prove that it is better at reducing pain than a sugar pill during short trials often lasting less than 12 weeks.



"Do they work for five years, 10 years, 20 years?" Dr. Portenoy said in the Journal interview. "We're at the level of anecdote." Even so, he says, the drugs can still benefit carefully selected patients.

Dr. Portenoy's ideas about opioids reached into mainstream medicine and attracted outspoken advocates. In a 1998 talk in Houston, Alan Spanos, a South Carolina pain specialist, said patients with chronic noncancer pain could be trusted to decide themselves how many painkillers to take without risk of overdose. According to a recording, Dr. Spanos said he understood that a patient would simply "go to sleep" before stopping breathing. While asleep, he said, the patient "can't take a dangerous dose. It sounds scary, but as far as I know, nobody anywhere is getting burned by doing it this way."

Dr. Spanos declined to say whether he still agreed with his previous statements. He said opioids can be helpful and safe with proper use.

One of Dr. Portenoy's chief complaints was that doctors were reluctant to prescribe opioids because they feared scrutiny by regulators or law enforcement. In the second half of the 1990s, he and his followers campaigned successfully for policies to change that.

In 1998, the Federation of State Medical Boards released a recommended policy reassuring doctors that they wouldn't face regulatory action for prescribing even large amounts of narcotics, as long as it was in the course of medical treatment. In 2004 the group called on state medical boards to make undertreatment of pain punishable for the first time.

That policy was drawn up with the help of several people with links to opioid makers, including David Haddox, a senior Purdue Pharma executive then and now. The federation said it received nearly $2 million from opioid makers since 1997. The federation says it derives the majority of its funding from administering medical licensing exams, credential verification, and data services.

A federation-published book outlining the opioid policy was funded by opioid makers including Purdue Pharma, Endo Health Solutions Inc. and others, with proceeds totaling $280,000 going to the federation. Endo declined to comment.

Purdue Pharma said, "Dr. Haddox was recruited by the FSMB, so he did not have undue or inappropriate influence" on the federation's output. Purdue declined to make Dr. Haddox available to comment.

The federation said it didn't believe its model policy contributed to increased prescriptions and said drug makers didn't influence its guidelines.

In 2001, the Joint Commission, which accredits U.S. hospitals, issued new standards telling hospitals to regularly ask patients about pain and to make treating it a priority. The now-familiar pain scale was introduced in many hospitals, with patients being asked to rate their pain from one to 10 and circle a smiling or frowning face.

The Joint Commission published a guide sponsored by Purdue Pharma. "Some clinicians have inaccurate and exaggerated concerns" about addiction, tolerance and risk of death, the guide said. "This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control."

Purdue said the booklet emerged from a process that "represented the consensus of a broad range of interested stakeholders." Drug makers regularly pay for educational materials for physicians as an element of their marketing.

The Joint Commission said its standards didn't encourage physicians and hospitals to increase prescriptions. "I think that's a very distorted and not helpful explanation of what's going on," said Ana McKee, the Joint Commission's chief medical officer.

Over his career, Dr. Portenoy has disclosed relationships with more than a dozen companies, most of which produce opioid painkillers. "My viewpoint is that I can have those relationships, they would benefit my educational mission, they benefit in my research mission, and to some extent, they can benefit my own pocketbook, without producing in me any tendency to engage in undue influence or misinformation," he said.

Dr. Portenoy and Beth Israel declined to provide details of their funding by drug companies. A 2007 fundraising prospectus from Dr. Portenoy's program shows that his program received millions of dollars over the preceding decade in funding from opioid

makers including Endo, Abbott Laboratories , Cephalon, Purdue Pharma and Johnson & Johnson .

Endo, Abbott, Janssen and Purdue declined to comment. Cephalon's current owner, Teva Pharmaceutical Industries Ltd. , didn't immediately have a comment.

In May of this year, the Senate Finance Committee opened an investigation into the financial ties between the pharmaceutical makers and the doctors and groups that advocated broader use of opioids. It asked opioid makers to disclose how much they had paid Dr. Portenoy, his program and several organizations he was involved with.

After spending most of his professional life advocating greater use of the drugs, Dr. Portenoy said there is still little research to show whether patients who embark on long-term opioid therapy will ever be able to stop.

Earlier this year, he said, he asked his mother whether she would stop taking her hydrocodone as part of a scientific study. She said no.

"How difficult is it for her to get off these drugs?" Dr. Portenoy asked. "You have no idea and neither do I, because no one knows."

—Devlin Barrett contributed to this article.

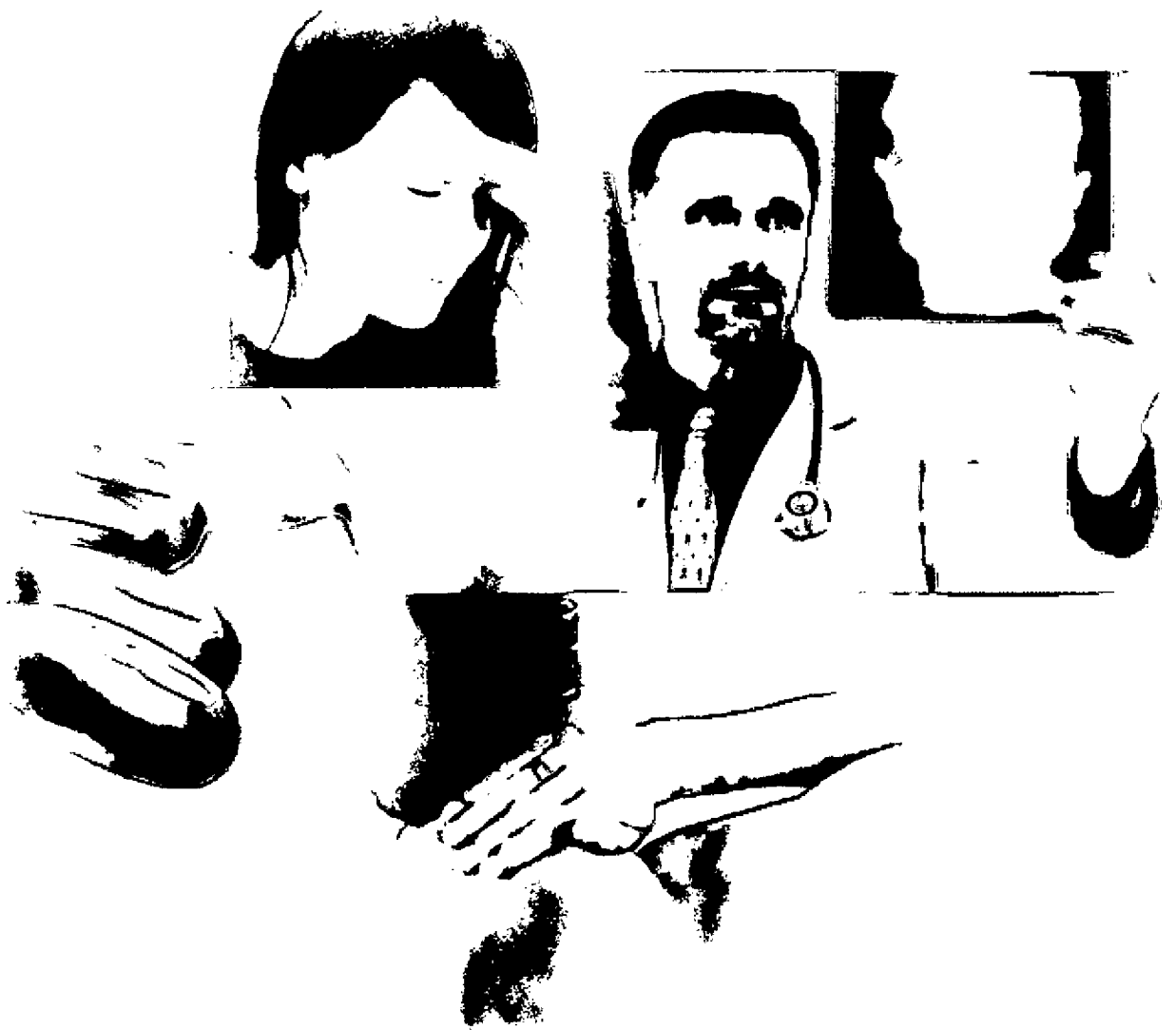
Write to Thomas Catan at thomas.catan@wsj.com and Evan Perez at evan.perez@wsj.com

Corrections & Amplifications

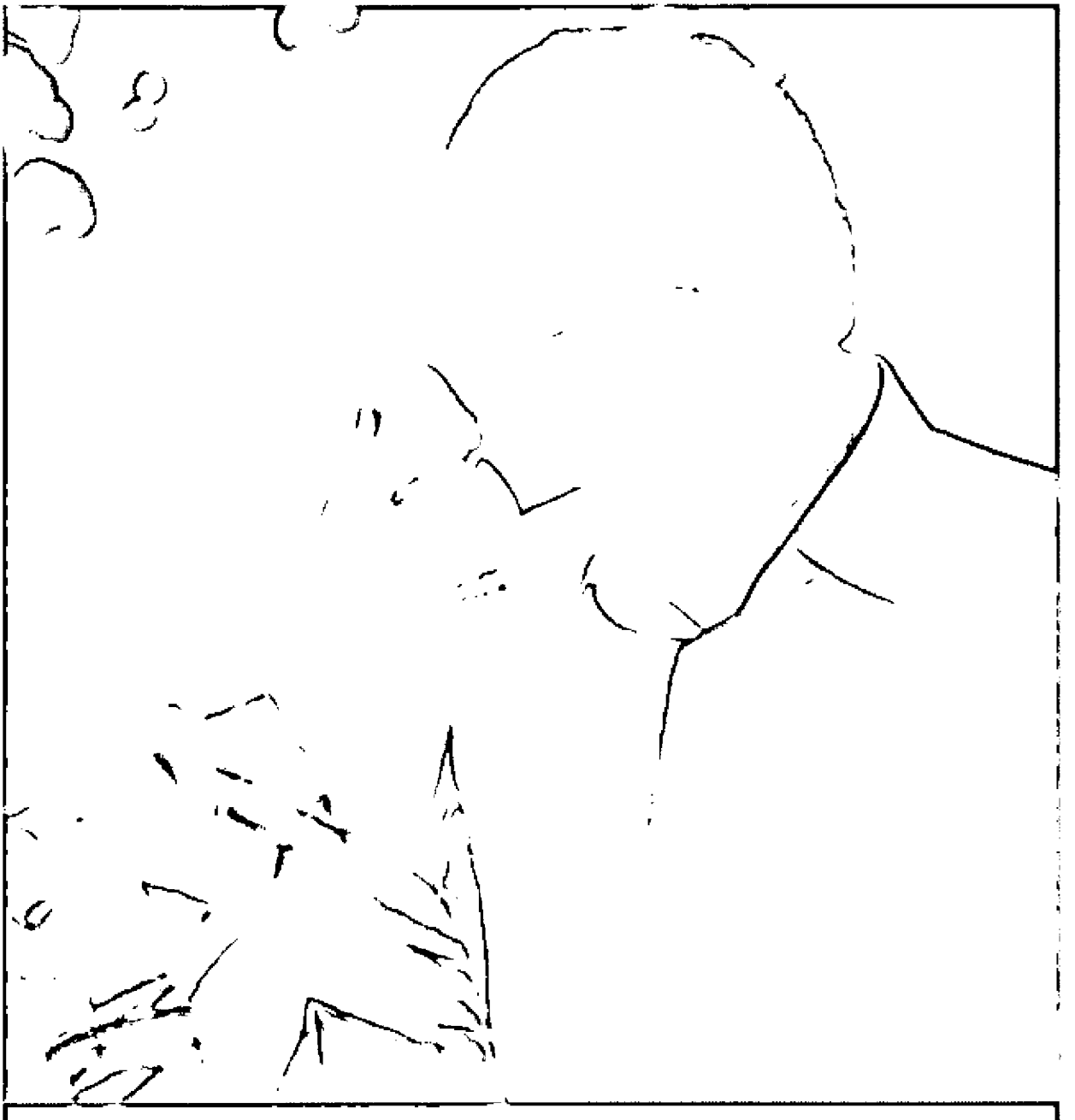
In the United States in 2010, there were 5.4 opioid-related deaths per 100,000 people and 5.4 admissions for treatment of opioid addiction per 10,000 people. An earlier version of a graphic accompanying this article reversed the labels on the two charts.

EXHIBIT E

American Pain Foundation
A United Voice of Hope and Power over Pain



A Reporter's Guide:
Covering Pain and Its Management



Pain is a complex perception that differs enormously from one person to another, even those with seemingly identical injuries or illnesses.

Introduction

Everyone has experienced pain—whether it's a pounding headache at the end of a long day, a throbbing toothache warning of a cavity or infection, an open wound or sprained ankle from a fall, or a stinging burn from touching a hot pan.

There are hundreds of pain syndromes, and pain is often a chief symptom of most chronic conditions, including cancer, diabetes, arthritis, fibromyalgia and a host of neurological disorders. For millions of Americans, pain persists, interfering with everyday activities and enjoyment of life. People living with chronic pain will often avoid certain movements or activities, fearful they will cause more injury or to avoid the anxiety of anticipated pain.

Pain is complex and frequently misunderstood by the public. The issue of pain is riddled with myths and misperceptions, which makes the task of informing and educating people about pain and its management that much more challenging.

SOME COMMON MISCONCEPTIONS ABOUT PAIN

- **Pain is "all in your head."** Although this is partially true because we need our brains for the perception of pain, that does not mean pain is imaginary when the source of pain is not well understood. Pain is all too real to the person who lives with it day in and out.
- **Pain is just something one has to live with**—an inevitable part of a disease or condition. The fact is most pain can be relieved with proper pain management.
- **Pain is a natural part of growing older.** While pain is more common as we age because conditions that cause pain (e.g., arthritis, degenerative joint diseases, cancer, shingles, osteoporosis) are more frequent in older adults, it should not be something people have to struggle with.
- **The best judge of pain is the physician or nurse.** Studies have shown that there is little correlation between what a physician or nurse might "guess" about someone's actual pain. The person with pain is the authority on the existence and severity of his/her pain. The self-report is most reliable indicator.
- **Seeking medical care for pain is a sign of weakness.** Pain carries a stigma, and many people hesitate talking about their pain and how it affects their daily life; they also don't want to be considered a "bad" patient.
- **Use of strong pain medication leads to addiction.** Many people living with pain and even some healthcare providers falsely believe opioids (strong pain medicines) are universally addictive. Studies have shown that the risk of addiction is small when these medicines are properly prescribed and taken as directed. As with any medication, there are risks, but these risks can be managed.

Key Reporting Challenges

A limited and informal survey of reporters, editors and producers revealed the following challenges when researching and covering the pain/pain management story:

- Stigma of pain management, especially among legal and government regulatory bodies
- Hesitancy on the part of patients and providers to discuss opioids for legitimate chronic pain management given misperceptions about opioids and addiction
- Ability to find unbiased, credible information about pain
- Limited number of randomized controlled trials
- Finding pain patients who live with the type of pain and/or use the pain management approach being reported in the news story
- Accurately characterizing the pain experience given that every person experiences pain differently, even if they have a similar injury or illness

THE UBIQUITOUS NATURE OF PAIN

Consider the following...

- Most Americans (80%) will suffer from back pain at some point in their lives.
- As we age, arthritis hinders the normally smooth sliding motion of our joints and connective tissues, resulting in stiffness and discomfort. Arthritis is the leading cause of disability in people over the age of 55.
- Pain associated with pediatric immunizations is a significant source of anxiety for children receiving the immunizations, and evidence suggests that the way children and parents cope can set the stage for future pain responses.
- Damage to or dysfunction of the central nervous system, due to stroke, multiple sclerosis, epilepsy, brain or spinal cord injuries or Parkinson's disease, also stimulates pain pathways.
- An estimated 30 to 50% of patients undergoing active treatment for cancer and 70% of those with advanced stages of the disease experience significant levels of pain and may be reluctant to discuss their pain with their doctors.

Sources: The American Academy of Physical Medicine and Rehabilitation, Arthritis Foundation, Mayday Fund, National Institute of Neurological Disorders and Stroke, National Cancer Institute.

Purpose of This Guide

The American Pain Foundation (APF) has developed this Guide as a primer on pain and pain management to help meet the informational needs of busy reporters, editors and producers covering the pain story. We know it's a complex topic, and hope you will find this to be a useful resource.

INSIDE YOU WILL FIND:

Page

- A basic overview of the burden of pain in America, consequences of unmanaged pain, pain assessment tools and treatment options *4*
- Pain Stats & Facts *10*
- Special Topic Briefs covering
  - *Special Considerations: Pain in Specific Populations* *13*
  - *Pain Management and Disparities* *23*
  - *Chronic Pain and Opioid Therapy* *27*
    At a Glance: Differentiating addiction, physical dependence and tolerance
  - *Integrative Medicine: Non-Drug Treatment Options for Pain Management* *35*
- Pain A to Z: Common Pain Terms and Syndromes *40*
- Online Pain Resource *43*

Be sure to visit the Newsroom section of the American Pain Foundation's web site at www.painfoundation.org to download additional copies and to check for posted updates and new Topic Briefs as they are added. Here you will also find recent news releases, press statements and background information on a wide variety of issues related to pain care.

ABOUT THE AMERICAN PAIN FOUNDATION

APF's mission is to improve the quality of life for people with pain by:

- Raising public awareness;
- Providing practical information, education and support;
- Advocating to remove barriers and increase access to effective pain management; and,
- Promoting research.

Since its founding in 1997, the American Pain Foundation (APF) has been at the forefront of advocating for people living with a wide variety of pain conditions and their caregivers.

Our grassroots effort, *Power Over Pain Action Network*, is now active in nearly 40 states and is comprised of people living with pain, caregivers, healthcare providers and advocates, who are working hard to call attention to the urgent need for positive changes in pain policy, practice and research investment.

EXPERTS AVAILABLE FOR INTERVIEW

APF can connect reporters with a wide array of leading pain experts, as well as people living with pain and their caregivers. Whether you are working on a national or local story, we can help coordinate interviews about pain-specific conditions and other important issues related to pain (e.g., depression, coping skills, financial matters, disparities, treatment options).

If you are interested in interviewing someone at APF or need additional resources, please contact Tina Regester, APF's communications manager, at (443) 690-4707 or tregester@painfoundation.org.

A Primer on Pain and Its Management

BURDEN OF PAIN IN AMERICA: AN EVOLVING PUBLIC HEALTH CRISIS

Pain is a serious and costly public health issue. It affects more Americans than diabetes, heart disease and cancer combined, and is a leading cause of disability in the United States. Even though pain is one of the most common reasons patients consult a healthcare provider, it is often inadequately assessed and treated, resulting in needless suffering and poor patient outcomes.

PAIN IS WOEFULLY UNDERTREATED FOR A VARIETY OF REASONS, INCLUDING:

- Misconceptions about opioid addiction
- Lack of access to care
- Cultural norms and the stigma associated with admitting pain
- Limited or no professional training in pain management, which leaves healthcare providers ill-equipped to effectively respond to patients' reports of pain
- Concerns among physicians about prescribing pain medications for chronic pain, and fears of scrutiny by regulators or law enforcement
- Inadequate funding for pain research (less than 2% of NIH research budget was dedicated to pain studies)

Untreated or poorly managed pain can compromise every aspect of life, including a person's physical and mental health, social and intimate relations, ability to sleep and perform everyday tasks, work productivity and financial well being.

Chronic pain is not only emotionally and physically debilitating for patients, it also places a tremendous burden on families and caregivers, and contributes to excessive healthcare costs. The economic toll of chronic pain exceeds $100 billion each year in the United States alone. As the 75 million Baby Boomers move toward retirement, the epidemic of untreated or undertreated pain is expected to continue.

More than one-quarter of Americans (26%) age 20 years and over—or, an estimated 76.5 million people—report that they have had a problem with pain. This number does not account for acute pain.

Source: National Center for Health Statistics, 2006.

PAIN BASICS

The International Association for the Study of Pain defines pain as: An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

COMMON PAIN CONDITIONS

- Headaches or migraine
- Back pain and sciatica
- Neck and shoulder pain
- Joint pain due to arthritis, bursitis, fibromyalgia or degenerative joint disease
- Muscle pain from overuse or strain, injury or fibromyalgia
- Post-surgical pain

For definitions of these and other pain conditions, as well as common pain terms, please refer to the Pain A to Z listing at the back of this resource.

At its best, pain is the body's natural alarm system, alerting us to injury (or further injury if already injured). It prompts us to stop a harmful behavior or seek medical attention. For example, lifting too much weight might result in a piercing pain in a person's back. Within moments of touching a hot surface, the fiery sensation of a burn warns us to quickly pull away. Worsening abdominal pain may be a sign of appendicitis or other serious infection. Pain also triggers inflammation, which directs healing cells to the area of injury. The experience of pain also beckons the injured person to rest, promoting healing.

At its worst, unrelenting pain robs people of their livelihood and well being. When pain persists, it is often a sign that the body's alert system has broken down. In other words, pain signals remain active. Over time, this heightened response may:

- Harm the nerves, blood vessels and organs
- Suppress immune function
- Result in excessive inflammation
- Delay healing

Since the brain remembers pain, pain may be imprinted into the nerve tissue and continue to send pain sensations even in the absence of painful stimuli.

Chronic Pain-Brain Connection

New research is unraveling how chronic activation of the biological pathways transmitting pain is associated with structural and chemical changes in the brain. A recent study suggests that constant pain signals can result in mental rewiring that affects the frontal cortex, the area of the brain mainly associated with emotion and attention. According to researchers, this provides the first objective proof of brain disturbances in patients with chronic pain that is unrelated to the sensation of physical pain.

ACUTE VS. CHRONIC PAIN

There are two main types of pain: acute and chronic.

	ACUTE PAIN	CHRONIC PAIN
Onset	Usually sudden	Sudden or gradual development
Cause	Typically linked to an event, such as an injury or disease	Contributing factors are less certain
Duration	Temporary (up to 3 months)	Persistent (beyond usual healing time or longer than 3 months)
Pain Identification	Painful areas are generally well identified	Painful areas are less easily differentiated
Pattern	Self-limiting or readily corrected	Continuous or intermittent; intensity may vary or remain constant
Course	Pain usually lessens over time	Pain usually increases over time
Response	Stress response may be present (increased heart and/or breathing rate, increase in blood pressure)	Stress response often absent
Prognosis	Total relief typically possible	Total relief often impossible

Adapted from: McCance K, Huether SE, eds. Pathophysiology: the biologic basis for disease in adults and children. 5th ed. New York, NY: Elsevier, 2006:447-489.

Acute Pain occurs suddenly due to illness, inflammation, injury or surgery. It has a short duration that subsides when the injured tissue heals. The cause of the pain can usually be diagnosed and treated.

Chronic Pain is pain that lasts long enough (after normal healing or for at least three months), or is intense enough, to affect a person's normal activities and well-being. Failure to treat acute pain promptly and appropriately at the time of injury, during initial medical and surgical care or at the time of transition to community-based care, contributes to the development of chronic pain syndromes.

With chronic pain, pain signals may remain active in the nervous system for weeks, months or even years. Unlike acute pain, chronic pain has no value or benefit; it is a disease in its own right. It can also be especially challenging to treat.

PAIN ASSESSMENT

Timely access to quality pain management is the best way to minimize the suffering and disability often associated with undertreated pain and to avoid additional problems down the road. Science is revealing the role of unrelieved acute pain in the development of chronic, persistent pain.

Most hospitals, nursing homes and other healthcare facilities are now required to assess and treat pain. To correctly diagnose pain, healthcare professional will:

- Perform a thorough physical exam
- Complete a pain assessment
- Ask detailed questions about the patient's medical history and lifestyle
- Order blood work, X-rays, electrical tests to detect nerve damage, or other diagnostic and laboratory tests

Pain is a subjective experience, and it is critical for healthcare professionals to have a complete picture of the patient's pain history. He/she may ask about seven characteristics of pain to help LOCATE the pain and make the correct diagnosis.

L the exact Location of the pain and whether it travels to other body parts
O Other associated symptoms such as nausea, numbness, or weakness
C The Character of the pain, whether it's throbbing, sharp, dull or burning
A Aggravating or Alleviating factors. What makes the pain better or worse?
T the Timing of the pain, how long it lasts, is it constant or intermittent?
E the Environment where the pain occurs, for example, while working or at home

The type of pain someone is experiencing is often a clue to its cause; for example, chronic pain that is burning or tingling is often the result of nerve disease (neuropathy).

EFFECTS OF UNRELIEVED CHRONIC PAIN ON PHYSICAL AND MENTAL HEALTH

If untreated, pain can have serious physiological, psychological and social consequences. It can:

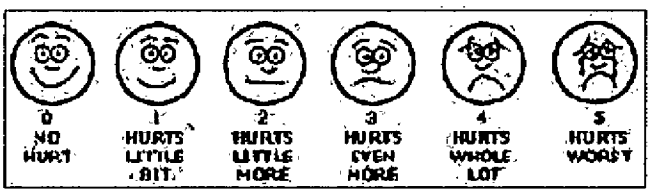
- Limit the ability to work, sleep, exercise or perform everyday tasks (for example, dressing, going to the grocery store)
- Reduce mobility
- Impair strength
- Diminish appetite
- Make it difficult to recover from an injury or fight infection by weakening the immune system
- Aggravate other health problems
- Lead to depression and/or anxiety, which often worsen pain sensations
- Make it difficult to concentrate or reason
- Place added strain on relationships and interfere with intimacy
- Result in a loss of self-esteem and independence

Pain scales are additional tools available to help patients describe the intensity of their pain. These assessment tools help healthcare professionals diagnose or measure a patient's level of pain. These include numeric, verbal or visual scales.

With **numerical scales**, patients use numbers from 0-10 (0 being no pain and 10 being the worst pain ever) to rate the intensity of the pain.

Verbal scales contain commonly used words such as "mild," "moderate" and "severe" to help patient's describe the severity of the pain.

Visual scales use aids like pictures of facial expressions, colors or gaming objects, such as poker chips, to help explain the severity of pain. One type, the Wong Baker Faces Pain Rating Scale, shows six different facial expressions from happy (no hurt) to agony (hurts the worst) to help show healthcare professionals how much pain a patient feels. Body diagrams may also be used to help pinpoint where the pain occurs.



From Hockenberry MJ, Wilson D, Winkelstein ML: *Wong's Essentials of Pediatric Nursing*, ed. 7, St. Louis, 2005, p. 1259. Used with permission. Copyright, Mosby.

Multidimensional pain assessment tools, such as the McGill Pain Questionnaire (MPQ) and the Brief Pain Inventory (BPI), have been developed to quantify different aspects of pain, including location and quality of pain and its effect on mood and function. However, these take longer to administer than the simpler scales and some patients who are cognitively impaired or poorly educated may find them difficult to complete. They are generally used in pain research, but can be adapted for clinical use if appropriate and valuable.

Our processing of pain is complex. A basic explanation is that the pain signals of acute pain are initiated when receptors on the skin, within an organ, tissue or nerve are triggered by injury or disease, known or unknown. A series of events follow: an electrical impulse, or pain message, is generated that is then carried on nerve fibers to the spinal cord. The spinal cord transmits the pain signal to various levels of the brain for interpretation and response. At any time during the transport of pain messaging, these noxious signals can be blocked, enhanced or modified. Signaling associated with chronic pain is much more complicated than acute pain as science is beginning to show.

TREATING PAIN

Successful pain management aims to:

1) lessen the pain
2) improve functioning and
3) enhance quality of life

Pain treatment needs to be individualized and, in most cases, requires a team of providers, as well as social support from family and friends. Most often, an integrative approach is needed to provide pain relief, which includes a combination of treatment options; this also encourages patients to actively participate in self-care. Treatment options may include:

- Medication (anti-inflammatory medicines, opioids or other classes of drugs)
- Psychosocial interventions (cognitive-behavioral counseling, guided imagery)
- Rehabilitative approaches (exercise, application of heat/cold, myofascial release, occupational therapy, if needed)
- Complementary alternative medicine (massage, acupuncture, hypnosis)
- Injection or infusion therapies
- Implantable devices and surgical procedures

Research shows that pain can affect patients' emotions and behavior and interfere with the ability to concentrate, manage everyday tasks and cope with stress. Likewise, stress and emotional pressures can make pain worse, provoking "flare ups" and contributing to alterations in the immune system response. These relationships are not always easily recognized or readily fixed by medical procedures or medications alone.

New treatments under investigation are aimed at the physical, psychological and environmental components of chronic pain. Research is also examining the role of genetic predisposition and the immune system in mitigating pain signals.

For a detailed description of the different treatment modalities for managing pain, please refer to the America Pain Foundation's *Treatment Options: A Guide for People Living with Pain.*

MEDICATIONS & PAIN MANAGEMENT

Medications play an important role in the treatment of pain. There are three major classes of medications for pain control:

Non-opioids: non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen

Opioids: morphine, oxycodone, methadone, codeine and fentanyl are examples

Adjuvant analgesics: a loose term referring to the many medications originally used to treat conditions other than pain, but now also used to help relieve specific pain problems; examples include some antidepressants and anticonvulsants. Some of these drugs have been shown to work well for specific types of pain.

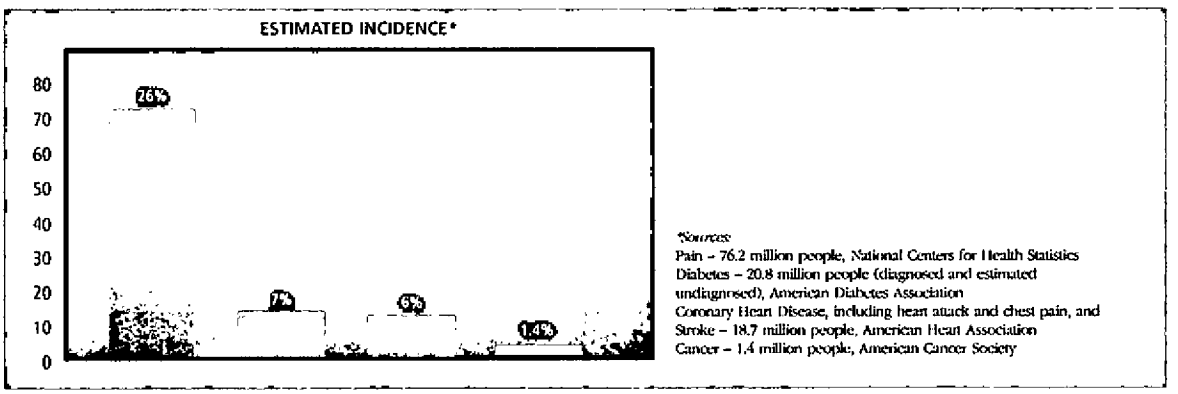
Drugs that have no direct pain-relieving properties may also be prescribed as part of a pain management plan. These include medications to treat insomnia, anxiety, depression and muscle spasms, and can help a great deal in the overall management of pain in some persons.

Pain Facts & Stats

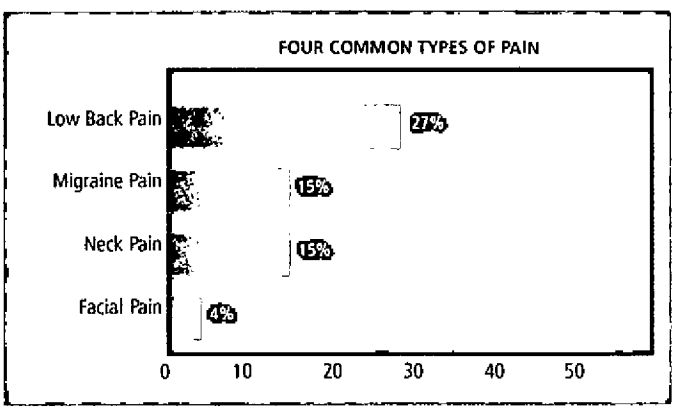
PREVALENCE OF PAIN

Pain is a serious and costly public health problem.

- A hallmark of many chronic conditions, pain affects more Americans than diabetes, heart disease and cancer combined.

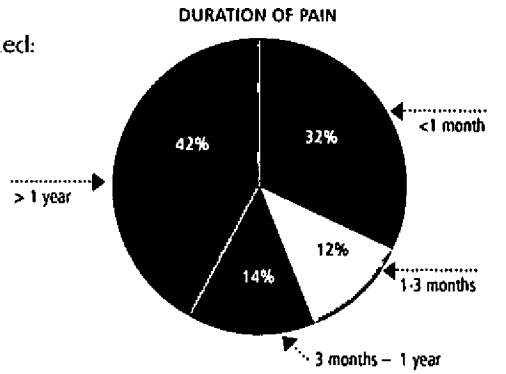


- More than one-quarter of Americans (26%) age 20 years and over—or, an estimated 76.5 million Americans—reported that they have had a problem with pain of any sort that persisted for more than 24 hours in duration. This number does not account for acute pain.[1]
- About one-third of people who report pain indicate that their pain is "disabling," defined as both severe and having a high impact on functions of daily life.[2]
- More women (27.1%) than men (24.4%) report that they are in pain.[1]
- Non-Hispanic white adults reported pain more often than adults of other races and ethnicities (27.8% vs. 22.1% Black only or 15.3% Mexican).[1]
- Adults living in families with income less than twice the poverty level reported pain more often than higher income adult.[1]
- When asked about four common types of pain, respondents of a National Institute of Health Statistics survey indicated that low back pain was the most common (27%), followed by severe headache or migraine pain (15%), neck pain (15%) and facial ache or pain (4%).[1]



DURATION OF PAIN

- Adults 20 years of age and over who report pain said that it lasted:
  - Less than one month – 32%
  - One to three months – 12%
  - Three months to one year – 14%
  - Longer than one year – 42%



ECONOMIC AND WORKPLACE BURDEN OF PAIN

- The annual cost of chronic pain in the United States, including healthcare expenses, lost income, and lost productivity, is estimated to be $100 billion.[3] However, more recent studies have indicated that costs associated with low back pain alone are an estimated $85.9 billion.[4] The total cost of arthritis—the nation's leading cause of disability—is estimated at $128 billion.[5]
- Undertreated pain drives up the cost of healthcare because it extends lengths of stay in hospitals, increases emergency room visits and results in unplanned clinic visits.
- Pain is the second leading cause of medically related work absenteeism, resulting in more than 50 million lost workdays each year.[6]
- Lost productive time due to headache, arthritis, back pain and other musculoskeletal conditions is estimated to cost $61.2 billion per year.[7]
  - Headache was the most common (5.4%) pain condition resulting in lost productive time. It was followed by back pain (3.2%), arthritis pain (2.0%), and other musculoskeletal pain (2.0%).
  - Most (76%) of the pain-related lost productive time was in the form of reduced performance occurring while the employees were at work, rather than absenteeism.
  - Workers who experienced lost productive time from a pain condition lost an average of 4.6 hours per week.

MUCH WORK REMAINS

- Currently, less than 2% of the NIH research budget is dedicated to pain.
- More than half of all hospitalized patients experienced pain in the last days of their lives and although therapies are present to alleviate most pain for those dying of cancer, research shows that 50-75% of patients die in moderate to severe pain.[8]

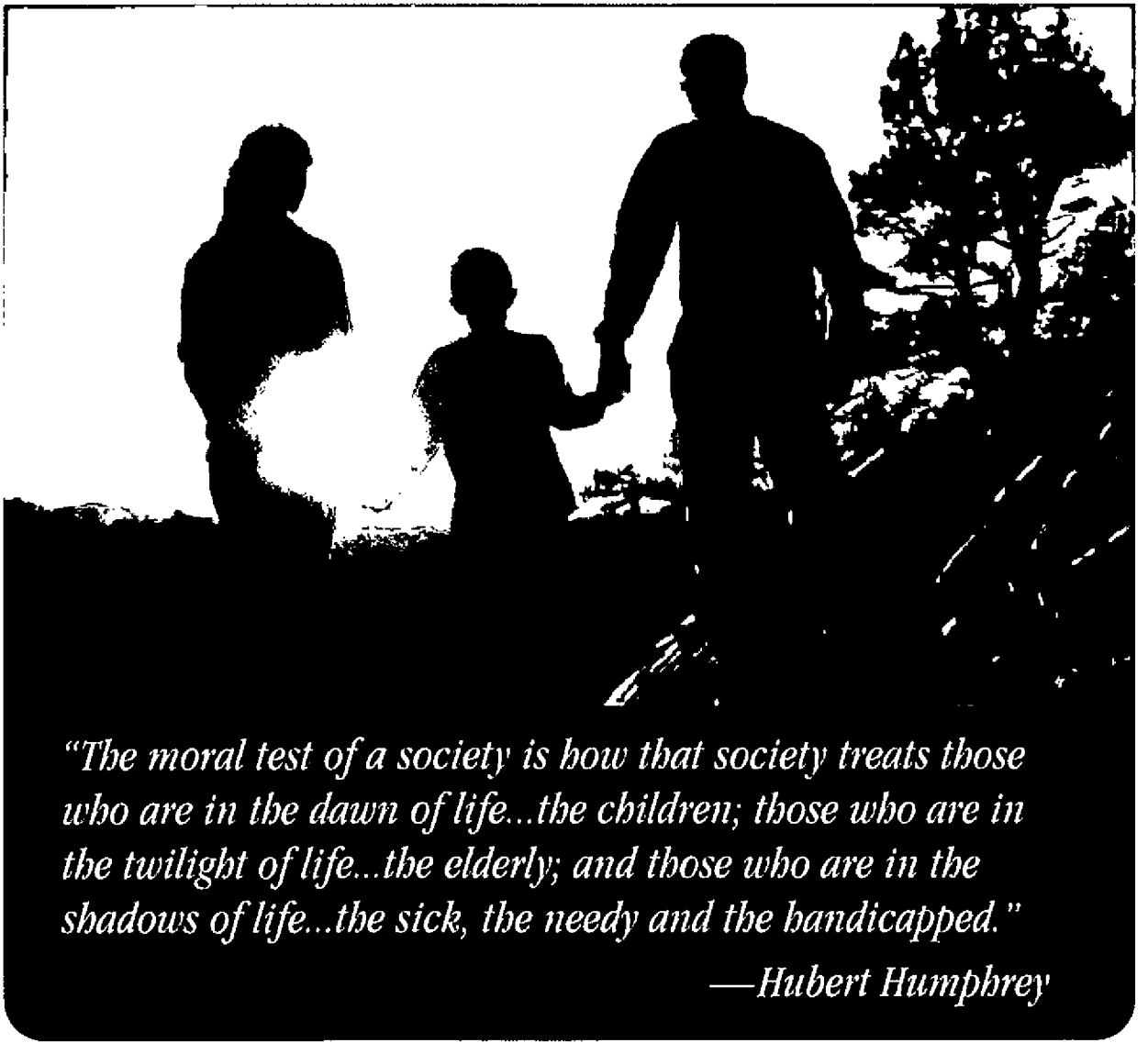
For more statistics and research findings, see our **Topic Briefs** on:

- Special Considerations: Pain in Specific Populations
- Disparities and Pain Management
- Integrative Medicine: Non-Drug Treatment Options for Pain Management
- Chronic Pain and Opioid Treatment

Be sure to visit the American Pain Foundation at www.painfoundation.org for posted updates and additional Topic Briefs.

REFERENCES

1. National Center for Health Statistics. Health, United States, 2006, Special Feature on Pain With Chartbook on Trends in the Health of Americans. Hyattsville, MD. Available at http://www.cdc.gov/nchs/data/hus/hus06.pdf.
2. Portenoy, R, Ugarte C, Fuller I, Haas G. "Population-based Survey of Pain in the United States: Differences Among White, African American, and Hispanic Subjects" *Journal of Pain*, Vol 5, Issue 6, 2004; pp 317-318.
3. National Institutes of Health. NIH Guide: New Directions in Pain Research I. September 4, 1998. Available from http://grants.nih.gov/grants/guide/pa-files/PA-98-102.html.
4. Brook I. Martin, MPH; Richard A. Deyo, MD, MPH; Sohail K. Mirza, MD, MPH; Judith A. Turner, PhD; Bryan A. Comstock, MS; William Hollingworth, PhD; Sean D. Sullivan, PhD. "Expenditures and Health Status Among Adults With Back and Neck Problems." JAMA. 2008;299(6):656-664.
5. Centers for Disease Control and Prevention. "Targeting Arthritis: Improving Quality of Life for More than 46 Million Americans." At a Glance 2008. Retrieved March 6, 2008 from http://www.cdc.gov/nccdphp/publications/aag/arthritis.htm.
6. American Pain Society. "Pain Assessment and Treatment in the Managed Care Environment." January 11, 2000. Available at http://www.ampainsoc.org/advocacy/assess_treat_mce.htm.
7. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost Productive Time and Cost Due to Common Pain Conditions in the US Workforce. *JAMA*. 2003;290:2443-2454.
8. Weiss SC, Emanuel LL, Fairclough DL, Emanuel EJ. Understanding the experience of pain in terminally ill patients. Lancet. 2001; 357:1311-1315.



SPECIAL CONSIDERATIONS: PAIN IN SPECIFIC POPULATIONS

Although pain is a significant problem among all Americans, certain populations are more susceptible to and at greater risk for undertreatment, including children, minorities and those with advanced, life-limiting medical illness. Studies conducted in emergency departments suggest that women receive less attention in response to reports of severe pain than men. As well, active duty military and veterans tend to experience pain differently and present greater challenges to achieving optimal pain relief.

In order to provide the most effective pain care possible and minimize pain-related morbidity, characteristics of vulnerable populations must be taken into consideration when performing pain assessment and implementing treatment plans. Healthcare professionals must also become aware of their own biases and understand that, regardless of demographic or social position, every individual with pain requires evaluation and treatment tailored to his or her specific clinical circumstances.

Children and Pain

Every child will experience pain at one time or another, whether it's from everyday bumps and bruises, or more chronic conditions such as headaches, gastrointestinal problems or diabetes. In fact, research shows that as many as 40% of children and adolescents complain of pain that occurs at least once weekly, and chronic pain affects at least 15 to 20% of children.[1] And pediatric pain stems from a wide range of chronic conditions:

- Each year, 1.5 million children have surgery, and many receive inadequate pain relief. In 20% of cases, the pain becomes chronic.[2]
- Of children aged 5 to 17 years, 20% suffer headaches.[2]
- More than one-third of children complain of abdominal pain lasting two weeks or longer.[3]
- Juvenille arthritis, which causes joint inflammation and aches, affects nearly 250,000 people under the age of 16 years.[4]
- By 2010, 1 in 1,000 U.S. children will be a survivor of childhood cancer and may have to deal with late and long-term effects of treatment (e.g., chronic fatigue and pain syndromes, nerve damage).[2]
- Recent evidence reveals reduced pain sensitivity is a common feature of children with autism and Asperger's syndrome.[2]
- Musculoskeletal pain can result from "growing pains," a normal occurrence in about 25 to 40% of children.[5]

COMMON CAUSES OF PAIN IN CHILDREN

- Scrapes and bruises
- Needlestick pain from immunizations (most children receive up to 24 immunizations by their 2nd birthday)
- Sports injuries (e.g., sprains, concussion, fractures)
- Chronic illnesses (e.g., sickle cell disease, Type I diabetes)
- Headaches
- Abdominal pain (e.g., ulcerative colitis)

According to the American Medical Association, children and infants are at increased risk of inadequate pain management, with age-related factors playing a major role. Physical and psychological changes that occur during childhood development can make understanding and managing pain in children significantly more complicated than treating pain in adults.

Many things affect the way a child experiences, communicates and responds to pain, including:

- Their age
- Their beliefs and understanding of what is causing the pain
- Their ability to cope
- Their activity and anxiety levels
- Previous experiences with pain and how they learned to respond
- Support from parents and siblings
  - Preliminary data suggest that a mother's anxiety may be transmitted more strongly to her daughters than her sons, resulting in increased anxiety and pain in girls, but not boys.[6]

If pain is not addressed and treated early on, it can greatly impact a child's quality of life by interfering with mood, sleep, appetite, school attendance, academic performance, and participation in sports and other extracurricular activities. Further, if unrelieved, childhood pain can enhance a child's vulnerability to pain later in life.[7] It is essential that healthcare providers begin to approach pediatric pain so that appropriate strategies can be devised to target and reduce

children's distress and pain-related disability.

Unaddressed pain can also result in significant financial stress for families who not only have to cover healthcare expenses, but who may also have to miss work to care for a sick child.[8]

Inadequate prevention and relief of pediatric pain are still widespread. Many obstacles exist to providing appropriate pain care to children and adolescents:[10]

- Beliefs and attitudes about the experience of pediatric pain.
- General lack of understanding about the best course of action for treating children in pain.
- Belief that pain should be treated less aggressively in children than adults.
- Pediatric pain management research has not been effectively translated into routine clinical practice.
- Pain in children with disabilities or other special health care needs may be more difficult to assess.

MYTHS AND TRUTHS ABOUT PAIN IN CHILDREN

MYTH: Children who are playing or sleeping must not be in pain.

TRUTH: Children cope with pain by distracting themselves, often through play. Sleep may also be a coping mechanism, and/or because they are exhausted.

MYTH: Young infants do not feel pain because their nervous systems are immature and unable to perceive and experience pain the way adults do.

TRUTH: Decades ago it was believed that a newborn couldn't feel pain, and surgery was routinely performed on infants without anesthetic. Today, we know that the central nervous system of a 26-week-old fetus has the capability of experiencing pain. There is strong evidence that children experience increasing anxiety and perception of pain with multiple procedures or painful stimuli.[8]

MYTH: Children can easily become addicted to pain medications.

TRUTH: Less than 1% of children treated with opioids become addicted.[9]

MYTH: Children cannot effectively communicate their pain; it is difficult to know when they have pain.

TRUTH: Children don't communicate, respond to, or feel pain the same way adults do, so it's difficult for health professionals and parents to understand what they are experiencing. But, it is very real and not something they easily forget about. There are many tools available to assess pain in children. Adults need to recognize how children of different ages express pain in both behaviors and words.

MYTH: Children will tell adults when they are having pain.

TRUTH: Children may not have the words to express pain (e.g., hurt, "ouch") or know to point to where it hurts. They may also be afraid of the consequences (e.g., extra visits to the pediatrician, shots, medicine).

Potential barriers to the effective treatment of pain in children[10]

- The myth that children, especially infants, do not feel pain the way adults do;
- Lack of routine assessment for the presence of pain in children;
- The idea that treating pediatric pain takes too much time and effort;
- Fears of adverse effects of analgesic medications, including respiratory depression and addiction;
- Differing personal values and beliefs of healthcare professionals about the meaning and value of pain in the development of the child (e.g., the belief that pain builds character).

WEB RESOURCES

American Pain Society
www.ampainsoc.org

National Children's Pain Center
www.pediatricpain.org/ncpc.php

Pediatric Pain Sourcebook
http://painsourcebook.ca/

UCLA Pediatric Pain Program
www.mattel.ucla.edu/pedspain/home.php

American Academy of Pediatrics
http://www.aap.org

Gender and Pain

Although it has long been thought that women and men have similar pain experiences, recent research reveals significant differences in the way male and female brains process pain,[1] as well as in women's expression of pain and their responsiveness to analgesics and pain stimulus.[2,3]

Historically, women have been categorized as being emotional and overly sensitive; often influencing the way physicians assessed and managed their pain.[4] Even though research now shows that chronic pain conditions are generally more prevalent among women, they continue to be treated less aggressively for their pain than men.[5,6] And while women are more likely than men to seek treatment for their pain, they are less likely to receive it.[7]

Women report pain more often than men do and in more body regions, and they also tend to have more severe, recurrent and persistent pain, as well as a reduced pain threshold when compared with men.[3] However, despite their increased pain burden, women reportedly cope with pain better than men, possibly due to the fact that they experience pain more often throughout the course of their lives (e.g., menstruation, pregnancy and child birth, and other health issues specific to women).[3]

Female hormones are also likely to play a role in pain perception. Some pain conditions like migraine tend to vary with a woman's menstrual cycle, and many of the observed gender differences in pain appear to diminish following the reproductive years.[8]

Hormones May Influence Pain Experience

- Estrogen administration in women and in men can increase the incidence of chronic pain conditions.[9,10]
- Variations in women's estrogen levels, like those that occur during the menstrual cycle or during pregnancy, may regulate the brain's natural ability to suppress pain.[11]
- Some pain conditions such as migraine and fibromyalgia tend to fluctuate with a woman's menstrual cycle.
- Observed gender differences in pain appear to diminish following menopause.

Additionally, cultural conditioning may impact the expression of pain among women and men. As children, girls are more likely to be permitted to express pain and show emotion than boys, and attitudes about the social acceptability of gender and pain often carry into adulthood.[3]

Potential Sources of Gender Differences in Pain

Biological factors including:

- sex hormones
- genetics
- anatomical differences

Psychosocial influences including:

- emotion (e.g., anxiety, depression)
- coping strategies
- gender roles
- cultural conditioning
- health behaviors
- use of healthcare services

As advances in brain imaging technology provide further insights into gender variations in the experience of pain, it is becoming evident that different pain experiences among men and women will call for different approaches to pain management.

Ongoing research is essential to achieve:

- A better understanding of the biological and psychosocial factors that influence gender differences in pain
- A greater appreciation of the different health needs of men and women
- More effective and targeted pain treatments for women

PAIN DISORDERS WITH HIGHER PREVALENCE IN WOMEN

- Migraine
- Irritable bowel syndrome
- Fibromyalgia
- Chronic pelvic pain
- Interstitial cystitis
- Temporomandibular joint disorder (TMJ)
- Breast pain (mastalgia)
- Autoimmune disorders (e.g. Lupus and Chronic Fatigue Syndrome)
- Rheumatoid arthritis
- Osteoarthritis

WEB RESOURCES

International Association for the Study of Pain: Real Women, Real Pain
www.iasp-pain.org

National Institutes of Health: Gender & Pain
http://painconsortium.nih.gov/genderandpain/summary.htm

National Women's Health Resource Center
www.healthywomen.org/

Society for Neuroscience: Gender & Pain
www.sfn.org/index.cfm?pagename=brainBriefings_gender_and_pain

Older Adults and Pain

As we age, pain becomes a more common problem due to the high prevalence of chronic and progressive pain-producing conditions associated with aging. It is estimated that up to 50% of older persons living in the community have pain that interferes with normal function, and 59 to 80% of nursing home residents experience persistent pain.[1,2] Alarmingly, being older than 70 is the leading risk factor for inadequate pain management.[3]

Diagnosing and treating pain in older adults can be challenging. Those 65 and older often present with multiple medical and nutritional problems, take multiple medications and have many potential sources of pain. Older persons with dementia or communication problems are at even greater risk of undertreatment of pain due to difficulties communicating their pain.[4] Use of certain medications in older patients becomes problematic because of physiological changes.[5]

The most common cause of persistent pain in older adults is musculoskeletal in nature, typically from osteoarthritis or other bone, joint and spine disorders. According to the Arthritis Foundation, arthritis affects up to 80% of older adults, who report being fearful of recurring pain and disability. But the predilection for painful conditions does not mean that older adults need to live with uncontrolled pain. Quite the opposite; older patients can be effectively treated, and in so doing, pain-related morbidity—and even premature mortality—can and should be obviated.

COMMON PAIN CONDITIONS IN OLDER ADULTS

- Arthritis
- Lower back and neck pain; vertebral compression fractures from osteoporosis
- Abdominal pain (e.g., gallstones, bowel obstruction, peptic ulcer disease, abdominal aortic aneurysm)
- Cancer-related pain (symptom of disease or effect of nerve damage from treatments)
- Neuropathic pain due to diabetes, herpes zoster ("shingles"), kidney disease or other medical problems
- Muscle cramps, restless leg pain, itchy skin and sores due to circulatory problems or vitamin D deficiency
- Fibromyalgia
- Complex Regional Pain Syndrome (CRPS), which develops after an illness or injury and often affects the leg, arm, foot or hand
- Injuries, especially from falls

WEB RESOURCES

Handbook of Pain Relief in Older Adults—An Evidence-Based Approach
By Gloth III, F. Michael
http://www.humanapress.com/Product.asp?txtCatalog=HumanaBooks&txtProductID=1-58829-217-7

American Medical Association
Assessing and Treating Pain in Older Adults
http://www.ama-cmeonline.com/pain_mgmt/module05/index.htm

American Geriatrics Society Foundation
The Management of Persistent Pain: Resources for Older Adults and Caregivers
http://www.healthinaging.org/public_education/pain

End-of-Life and Pain

Pain control is one of the most challenging aspects of end-of-life care.[1] Terminal illness is often accompanied by severe pain, and a significant number of patients suffer needlessly at the end-of-life. While the goal of end-of-life care should be making patients more comfortable, the health care system has been designed to take a curative approach to disease, rather than focusing on symptom relief.[2] Hospital research reveals that healthcare providers continue to inadequately treat pain, and tend to under-medicate terminal pain.

Patients at end-of-life may have their pain undertreated for variety of reasons, including a lack of knowledgeable and experienced physicians and myths about addiction to pain medication, leading unnecessarily to patient and family suffering.[3]

Despite advances in research on end-of-life pain treatment, physicians remain influenced by social and legal concerns, as well as misconceptions about medications including addiction, overdose, lasting side effects and diminished physical capacity.[5] Patients and their families may also hesitate to begin using pain medications as they often associate such treatment with imminent death, thereby allowing patient suffering to worsen and continue.[4]

However, thorough and ongoing pain assessment, paired with well-designed and aggressive medication plans, as well as counseling for patients and their families can have a significant impact on pain relief and side effects among dying patients.[4,5]

IN DYING PATIENTS, PAIN MAY BE EXACERBATED BY MANY OTHER SYMPTOMS INCLUDING:

- Dry mouth
- Nausea
- Water retention and swelling
- Lack of appetite
- Shortness of breath
- Mental distress and anxiety caused by fear or denial of impending death

Effective pain management at the end-of-life requires addressing the total pain experience, including physical causes, as well as interpersonal and spiritual pain.[3,4]

Pain associated with terminal illness often requires special treatment that can be best provided by hospice and palliative care programs available in many medical facilities. Hospice focuses on relieving symptoms and supporting patients who are nearing the end of their life, while palliative care is designed to provide comfort and pain relief at any time during a person's illness.[7] The goal of both programs is to alleviate suffering and ultimately assist patients in achieving a pain-free and dignified death.

"When someone is dying, time is a luxury and wait-and-see is not an option. What matters most in the final days is that patients are free of crippling pain and unbearable suffering so that they can finish their lives in ways that bring comfort, peace, and completion. Concerns about lasting side effects or diminished physical capacity from months of using a drug become secondary to making a patient comfortable. No one has to die in pain."

— Dr. Scott Fishman

"Suicidal wishes in patients with advanced disease are closely linked to unrelieved pain and to mood alterations such as depression and anxiety, which like pain, frequently respond to clinician treatment if the clinician identifies and addresses them."[26]

Essential Components of End-of-Life Care[8]

- Continual assessment and management of pain and other physical symptoms
- Assessment and management of psychological and spiritual needs
- Helping patients identify personal goals for pain treatment and end-of-life care
- Assessment of the patient's support system

WEB RESOURCES

American Academy of Family Physicians: Challenges in Pain Management at the End of Life
www.aafp.org/afp/20011001/1227.html

American Pain Society: Treatment of Pain at the End of Life
www.ampainsoc.org/advocacy/treatment.htm

Discovery Health Center: End of Life Q&A with Dr. Scott Fishman
http://health.discovery.com/centers/pain/endoflife/endoflife.html

National Hospice and Palliative Care Organization
www.nhpco.org/i4a/pages/index.cfm?pageid=3254

Military/Veterans and Pain[1]

Pain is a major issue among military personnel and veterans, who are at heightened risk for injury and combat wounds. Although today's body armor and rapid evacuation to medical care is saving lives, there are more maimed and shattered limbs than ever before, with instances of amputation double previous rates. Hundreds of thousands of returning veterans will seek medical care and claim disability compensation for a wide variety of injuries and health problems they endured during their tours of duty. It is estimated that the U.S. will be paying the cost of related medical care and disability claims for the next 40 years.

Veterans are more likely to experience psychological distress and other medical conditions, including post traumatic stress disorder, depression, amputations, traumatic brain injuries, substance abuse and other injuries, which further complicate effective pain management.

COMMON PAIN CONDITIONS AMONG MILITARY MEMBERS

Post traumatic stress disorder (PTSD) commonly affects soldiers returning from war, and is triggered by exposure to a situation or event that is or could be perceived as highly threatening to a person's life or those around him/her. PTSD may not emerge for years after the initial trauma. Chronic pain symptoms and PTSD frequently co-occur and may intensify an individual's experience of both conditions. Together, they result in fear, avoidance behaviors, anxiety and feelings of isolation.

Amputations have long been a tragic, unavoidable consequence of combat injury—"one of the most visible and enduring reminders of the cost of war," according to the Amputee Coalition of America. While there have been major advances in medicine, prosthetics and technologies that allow amputees to lead more independent lives, most of these patients continue to need specialized long-term or lifelong support. Managing wound, post-operative, phantom and stump pain is important to reduce suffering and improve quality of life.

A traumatic brain injury (TBI) is a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain and is a major cause of life long disability and death. Managing pain in veterans with TBIs may be complicated by memory lapses affecting medication management, difficulty organizing and following complicated and sometimes even simple pain management regimens, and difficulty learning new coping skills. Rehabilitation should incorporate efforts to relieve associated pain.

Veterans have significantly worse pain than the general public, and while military medical care is among the best in the world, there are still long-term problems and challenges with managing disability and chronic pain.

Military culture may also present a significant barrier to appropriate patient care. The persisting stigma around pain and pain treatment is particularly pronounced in the military, and pain is often perceived as a sign of weakness leading many individuals to choose to suffer in silence. Seeking mental health care for PTSD and depression, which so often accompany pain is important; pain is best managed when depression and PTSD are treated simultaneously.

A recent analysis found that the Veterans Health Administration (VHA) is already overwhelmed by the sheer number of returning veterans and the seriousness of their health care needs. Without increased staffing and funding for veterans medical care, it will not be able to provide quality care in a timely fashion.

Military/Veterans and Pain[1]

Barriers to optimal pain management among veterans and military personnel may include fears about:

- No longer being physically capable of fulfilling their duties
- Being discharged and no longer having a sense of purpose
- Letting down or losing the respect of their peers
- Becoming addicted to pain medications
- Experiencing personality changes or problems with sexual relations due to pain medications
- Losing their benefits/pension if they acknowledge a pain condition

THE UNITED STATES CONGRESS HAS STATED THE FOLLOWING:

(1) Acute and chronic pain are prevalent conditions among active duty and retired military personnel.

(2) Characteristics of modern warfare, including the use of improvised explosive devices, produce substantial numbers of battlefield casualties with significant damage to both the central and peripheral nervous systems.

(3) The successes of military health care both on and off the battlefield result in high survival rates of severely injured military personnel who will be afflicted with significant pain disorders on either an acute or chronic basis.

(4) Failure to treat acute pain promptly and appropriately at the time of injury, during initial medical and surgical care, and at the time of transition to community-based care, contributes to the development of long-term chronic pain syndromes, in some cases accompanied by long-term mental health and substance abuse disorders.

(5) Pain is a leading cause of short- and long-term disability among military personnel.

(6) The military health care systems have implemented important pain care programs at some facilities and in some areas, but comprehensive pain care is not consistently provided on a uniform basis throughout the systems to all patients in need of such care.

(7) Inconsistent and ineffective pain care leads to pain-related impairments, occupational disability, and medical and mental complications with long-term costs for the military health and disability systems, and for society at large.

(8) Research, diagnosis, treatment, and management of acute and chronic pain in the active duty and retired military populations constitute health care priorities of the United States.

From the Military Pain Care Act of 2008

The U.S. Veterans Health Administration is instructing physicians and nurses who treat veterans to regard pain as a "fifth vital sign," to be routinely assessed along with blood pressure, pulse, temperature and respiration.

WEB RESOURCES

American Pain Foundation: Military/Veterans and Pain
www.painfoundation.org/page.asp?file=Veterans/Intro.htm

Amputee Coalition of America
www.amputee-coalition.org

Defense and Veterans Brain Injury Center
www.dvbic.org

Disabled American Veterans (DAV)
www.dav.org

Military Pain Care Act of 2008
http://www.govtrack.us/congress/bill.xpd?bill=h110-5465

U.S. Department of Veterans Affairs
www.va.gov

HOT TOPICS

Children & Pain: HOT TOPICS

- Maternal anxiety influencing daughters' experience of pain
- Some neonatologists still do not treat pain in pre-term low birth weight babies because they "won't remember it"
- Investigations into "chronic daily headaches" in children
- Unraveling pediatric pain conditions and their impact into adulthood (e.g., whether Complex Regional Pain Syndrome in children leads to adult CRPS, whether irritable bowel syndrome in adolescents is this the same as IBS in adults)
- Complementary and alternative medicine: how and what is safe to use in children with chronic pain?
- Factors leading to pain-related disability in children (e.g., missing school, not sleeping, avoiding physical and social activities, not eating)

Gender & Pain: HOT TOPICS

- Prevalent pain conditions in women (e.g., fibromyalgia, chronic pelvic pain)
- Interface of hormones and the pain experience
- Brain imaging, uncovering routes of pain transmission and tolerance
- Differential effects of medicines across genders
- Impact of chronic pain on sexuality and self-image

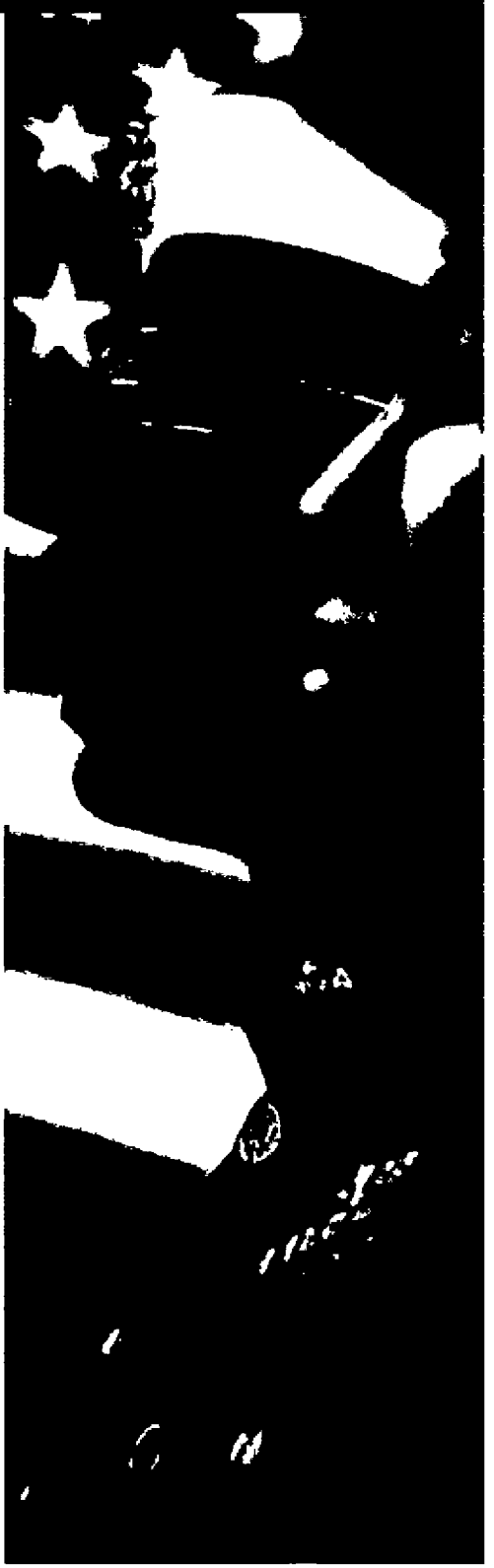
HOT TOPICS

Older Adults and End-of-Life Care & Pain: HOT TOPICS

- False belief that pain is an inevitable part of aging
- Vitamin deficiencies and musculoskeletal pain
- Limited consumer awareness of the options that exist other than traditional "acute care" approaches (e.g., doctor's office visits, ER visits, hospitalizations)
- Insufficient numbers of adequately trained and skilled healthcare professionals to manage the myriad issues confronting patients/families with advanced medical illness; limited number of providers with specialty in geriatrics
- Variability in delivery of hospice and palliative care services across the country
- Lack of clinical research data on pain care among elders

Military/Veterans & Pain: HOT TOPICS

- President Bush recently signing the Military and Veterans Pain Care Acts into law
- Emerging Options: Interdisciplinary approaches to pain care
- Acupuncture now being incorporated into treatment plans at Walter Reed Army Medical Center
- Competitive athletics as a form of therapy
- New Veteran centers open for drop-in counseling



References

Children and Pain

1. Goodman, JE, McGrath, PJ. (1991). The epidemiology of pain in children and adolescents: A review. *Pain*, 46:247–264.
2. Zeltzer LK, Schlank CB. (2005) Conquering Your Child's Chronic Pain: A Pediatrician's Guide for Reclaiming a Normal Childhood. New York, NY: HarperCollins.
3. *Chronic Abdominal Pain in Childhood: Diagnosis and Management*. Retrieved October 12, 2008 from American Academy of Family Physicians. Web site: http://www.aafp.org/afp/990401ap/1823.html
4. Juvenile Arthritis. Retrieved October 13, 2008 from American Academy of Orthopaedic Surgeons. Web site:http://orthoinfo.aaos.org/topic.cfm?topic=A00075
5. Nemours Foundation. Growing Pains Fact Sheet. Retrieved October 13, 2008 from http://kidshealth.org/parent/general/aches/growing_pains.html.
6. Tsao JCI, Lu Q, Kim SC, Zeltzer LK. (2006). Relationships among anxious sympto-matology, anxiety sensitivity and laboratory pain responsivity in children. *Cognitive Behaviour Therapy*, 35:207-215.
7. Zeltzer LK, Anderson CTM, Schechter NL. (1990) Pediatric Pain: Current status and new directions. *Current Problems in Pediatrics*, 20(8):415-486.
8. Anand KJS. (2006). Fetal pain. *Pain-Clinical Updates*, 14:1-4.
9. Foley KM. (1996) Controlling the pain of cancer. *Sci Am*, 275(3): 164-165.
10. *The Assessment and Management of Acute Pain in Infants, Children, and Adolescents: A Position Statement from the American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and American Pain Society Task Force on Pain in Infants, Children, and Adolescents.* Retrieved October 12, 2008 from American Pain Society. Web site: http://www.ampainsoc.org/advocacy/pediatric2.htm

Gender and Pain

1. Paulson PM, Minoshima S, Morrow TJ, Casey KL. (1998) Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. *Pain*, 76:2239.
2. Fillingim RB, Maixner W. (1995) Gender differences in the response to noxious stimuli. *Pain Forum*,4:209-21.
3. Berkley KJ. (1997) Sex differences in pain. *Behav Brain Sci*, 20:371-80.
4. Fishbain DA, Goldberg M, Meagher BR, et al. (1986) Male and female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria. *Pain*, 26(2):181-97.
5. LeResche L. (1999) Gender considerations in the epidemiology of chronic pain. Chapter in I. Crombie (ed.), *Epidemiology of Pain*. IASP Press, Seattle.
6. Green CR. "Pain, Disparities, and Practice: Opportunities to Improve Health Policy and Healthcare Quality," Presented September 9, 2008 at the American Academy of Pain Management annual meeting.
7. Hoffmann DE, Tarzian AJ. (2001) The Girl Who Cried Pain: A Bias Against Women in the Treatment of Pain. *J Law Med Ethics*, 29:13-27.
8. Gagliese L, Fillingim RB. (2003) Age and sex interactions in the experience of pain. XX vs. XY: *The International Journal of Sex Differences in the Study of Health, Disease and Aging* 1,124131.
9. Dao TT, LeResche L. (2000) Gender differences in pain. *J Orofac Pain*, 14: 169184.
10. Aloisi AM, Bachiocco V, Costantino A, Stefani R, Ceccarelli I, et al. (2007) Crosssex hormone administration changes pain in transsexual women and men. *Pain*. [Epub ahead of print]
11. Zubieta JK. "Systems Integration and Neuroimaging in the Neurobiology of Pain" Presented February 18, 2003 at the American Association for the Advancement of Science annual meeting.

Older Adults and Pain

1. Ferrell BA. (1995). Pain evaluation and management in the nursing home. *Ann Intern Med*, 123:681-687.
2. Helme RD, Gibson SJ. Pain in Older People. In: Crombie IK, ed. *Epidemiology of Pain*. Seattle: IASP Press; 1999:103-112.
3. Cleeland, CS, Gonin R, Hatfield AK, Edmonson JH, et al. (1994) Pain and Its Treatment in Outpatients with Metastatic Cancer. *N Engl J Med*, 330(9):592-596.
4. Parmalee PA, Smith B, Katz IR. (1993). Pain complaints and cognitive status among elderly institution residents. *J Am Geriatr Soc*, 41:517-22.
5. Schmucker DL. (2001) Liver Function and Phase 1 Drug Metabolism in the Elderly: A Paradox. *Drugs Aging*, 18:837-851.

End-of-Life and Pain

1. *Challenges in Pain Management at the End of Life.* Retrieved October 13, 2008 from American Academy of Family Physicians. Web site: http://www.aafp.org/afp/20011001/1227.html
2. *Treatment of Pain at the End of Life: A Position Statement from the American Pain Society.* Retrieved October 12, 2008 from American Pain Society. Web site: http://www.ampainsoc.org/advocacy/treatment.htm
3. *Pain Management at the End of Life: A Physician's Self-Study Packet.* Retrieved October 12, 2008 from Maine Hospice Council. Web Site: http://www.mainehospicecouncil.org/Pain%20Management%20web%20version.pdf
4. Leleszi JP, Lewandowski JG. (2005) Pain Management in End-of-Life Care. *J Am Osteopath Assoc*, 105(3_suppl), 6S-11.
5. *Pain Mangement: Q&A with Dr. Scott Fishman.* Retrieved October 12, 2008 from Discovery Health. Web site: http://health.discovery.com/centers/pain/endoflife/endoflife.html
6. Foley KM. (1995) A review of ethical and legal aspects of terminating medical care. *Amer J Med*, 84:291-301.
7. *End-of-Life Care.* Retrieved October 12, 2008 from National Hospice and Palliative Care Organization. Web site: http://www.nhpco.org/i4a/pages/index.cfm?pageid=3254
8. *End-of-Life Care Eases Pain and Prepares Patient for Death.* Retrieved October 12, 2008 from Medical College of Wisconsin. Web site: http://healthlink.mcw.edu/article/1001710698.html

Military/Veterans and Pain

1. *Military/Veterans and Pain* Fact Sheet. Retrieved October 13, 3008 from the American Pain Foundation. Web site: www.painfoundation.com.

Topic Brief

PAIN MANAGEMENT & DISPARITIES

The undertreatment of pain in America is a growing public health crisis, especially among underserved populations, including ethnic minorities, women, the elderly and those who are socioeconomically disadvantaged. Despite an overall improvement in health for most Americans, certain segments of the population continue to experience poor health status.[1] There is compelling evidence that minorities are less likely to have access to routine, coordinated medical care or health insurance than whites. They are also more likely to receive inappropriate or insufficient care, resulting in poorer health outcomes.

As the U.S. population becomes increasingly diverse, there is an urgent need to eliminate health disparities. Patients have a right to appropriate assessment and treatment of their pain without regard to race, ethnicity or other factors.

"Of all the forms of inequality, injustice in health is the most shocking and the most inhumane."
–Martin Luther King, Jr.

Health Disparities Defined

According to the National Institutes of Health, health disparities are defined as "differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States."

Disparities in health care are complex and multifaceted resulting from:

- Patient/personal factors (e.g., low socioeconomic status, communication barriers)
- Healthcare provider factors (e.g., bias, cultural insensitivity)
- Systematic/health system factors (e.g., health insurance status, access to care)

Snapshot of U.S. Population, An Older and More Diverse Nation

According to projections by the U.S. Census Bureau:

- Minorities now comprise roughly one-third of the U.S. population.
- By 2023, more than half of all children will be from minority groups.
- Minorities are expected to become the majority in 2042.
- In 2050, the nation is projected to be 54% minority.
- The Latino population, already the nation's largest minority group, will triple in size between 2005 and 2050.
- The nation's elderly population will more than double in size from 2005 through 2050 as the baby boom generation enters traditional retirement years.

Source: U.S. Census Bureau, 2008, http://www.census.gov/PressRelease/www/releases/archives/population/012496.html; Pew Hispanic Center.

Disparities in Pain Care

Pain is widely recognized as an undertreated health problem in the general population.[2] However, a growing body of research reveals even more extensive gaps in pain assessment and treatment among racial and ethnic populations, with minorities receiving less care for pain than non-Hispanic whites.[3,4,5,6]

Differences in pain care occur across all types of pain (e.g., acute, chronic, cancer-related) and medical settings (e.g., emergency departments and primary care).[3,4,5,6,7] Even when income, insurance status and access to health care are accounted for, minorities are still less likely than whites to receive necessary pain treatments.[3,4,8]

Minorities are less likely to:

- Have access to pain management services and treatments
- Have their pain documented by healthcare providers
- Receive pain medications

And more likely to:

- Use the emergency department for pain care, but less likely to receive adequate care
- Experience greater severity of pain
- Experience and report physical disability
- Experience poorer health and quality of life related to pain

There are clear variations in the way pain is assessed and managed among all minority populations. Significant gaps exist in the provision of effective quality pain care due to the lack of research and medical training focused on pain care disparities.[3,4,9]

Research also shows gender differences in the experience and treatment of pain. Most chronic pain conditions are more prevalent among women; however, women's pain complaints tend to be poorly assessed and undertreated.[3]

Additionally, gender differences have been identified in patient responsiveness to analgesics and pain stimuli. While estrogen and progesterone play a role in how pain signals are received in men and women, psychology and culture may also account for some of the difference. For example, children may learn how to respond to pain later in life depending on how their pain complaints were treated in their formative years (e.g., receiving comfort and validation versus being encouraged to tough it out or dismiss the pain).[14] For more information, see the *Special Considerations: Pain in Specific Populations* Topic Brief.

In response to the overwhelming discrepancies in pain treatment among minority groups, the Joint Commission issued a statement recognizing the rights of all patients to receive appropriate assessment and management of pain, and the World Health Organization has declared that pain relief is a human right.

RESEARCH ON DISPARITIES IN PAIN CARE HAVE SHOWN:

- Blacks were less likely than whites to receive pain medication and had a 66% greater risk of receiving no pain medication at all.[5,6,7,9]
- Hispanics were twice as likely as non-Hispanic whites to receive no pain medication in the emergency department (55% of Hispanics received no pain medication vs. 26% of non-Hispanic whites).[7,10]
- Minority patients were less likely to have pain recorded relative to whites, which is critical to providing quality patient care.[11]
- Only 25% of pharmacies in predominantly nonwhite neighborhoods had opioid supplies that were sufficient to treat patients in severe pain, as compared with 72% of pharmacies in white neighborhoods.[12]
- In a study of minority outpatients with recurrent or metastatic cancer, 65% did not receive guideline-recommended analgesic prescriptions compared with 50% of nonminority patients ($P < 0.001$). Hispanic patients in particular reported less pain relief and had less adequate analgesia.[13]

Patient and provider factors drive pain disparities

Multiple factors contribute to racial and ethnic disparities in pain care, including beliefs about pain, preconceived bias and cultural insensitivity and poor patient-provider communication.

Positive physician-patient interaction and communication is critical in accurate pain assessment.[2] Some research has shown that patients take a more active role in their own pain treatment when their healthcare providers are of similar ethnic backgrounds.[3,4]

"Pain is a complex, subjective response with several quantifiable features, including intensity, time course, quality, impact, and personal meaning. The reporting of pain is a social transaction between caregiver and patient."[15]

Patient sources of racial and ethnic disparities:[3]

- Low socioeconomic status
- Patients' attitudes or beliefs regarding pain and patient-level decision making and preferences
  - Stoicism and the belief that pain is an inevitable part of disease
- Minority patients more likely to:
  - Refuse recommended pain therapies
  - Poorly adhere to treatment regimens
  - Delay seeking medical care
- Mistrust of physicians or previous negative experiences with health care system
- Limited health literacy
- Language barriers that hinder communication with providers

Physician sources of racial and ethnic disparities:[3]

- Perceptions of race and ethnicity
- Racism or bias
- Poor cross cultural communication skills/cultural insensitivity
- Underrepresentation of physicians from racially/ethnically diverse backgrounds/lack of cultural sensitivity

HOT TOPICS

Disparities & Pain: HOT TOPICS

- Aging and increasingly diverse U.S. population could lead to greater disease burden if pain remains untreated
- Undertreatment of minorities in emergency departments
- Minority pain complaints receive less attention than others
- Impact of pain on productivity and quality of life among minority patients
- Pain relief as a human right

Minorities lack access to effective pain care

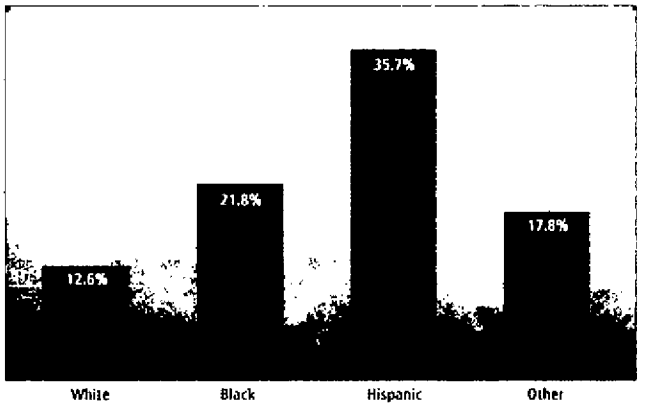
Limited access to pain care services is a key contributor to poorer pain treatment among minorities.

- Overall, minorities tend to be financially poorer than non-Hispanic whites.
- Socioeconomic factors can impede access to health insurance and primary health care services, and minorities are less likely to have access to pain treatment services than the general population.[3,4,7,16,17]
- Racial and ethnic minorities are at increased risk of having their pain complaints ignored by healthcare providers, thereby limiting their options for accessing appropriate pain treatment.[3,4,6,7]

According to the Robert Wood Johnson Foundation, 46 million Americans, including 9 million children, are living without health care coverage. More than eight out of 10 are from working families. The consequences of being uninsured are widely recognized and include: lack of access to health care, poor quality care, lost economic productivity, as well as financial burdens on individuals and society overall. As the minority population in the U.S. continues to grow, it becomes increasingly important to address the numbers of uninsured and underinsured among racial and ethnic groups.

Barriers also exist in patient access to pain medications. Research shows that physicians may be less likely to prescribe pain medications for minority populations [6,7,16,18] and pharmacies in neighborhoods with large minority populations often do not carry opioid medications.[3,4,12]

PERCENTAGE UNINSURED AMONG THE NONELDERLY POPULATION BY RACE AND ETHNIC ORIGIN, 2006



Sources: Employee Benefit Research Institute estimates from the March Current Population Survey, 2007 Supplement. Cover the Uninsured, www.coveruninsured.org.

"Inequities in access can contribute to and exacerbate existing disparities in health and quality of life, creating barriers to a strong and productive life."

—The Commonwealth Fund

More extensive research needed to close disparities gap

While national attention has become increasingly focused on health disparities, less attention has been given specifically to inequities in pain care.[19,20] However, the growing interest in health disparities in general provides pain treatment providers, researchers and advocates with an opportunity to raise awareness about disparities in pain management and the need for additional pain disparities research. Currently, the social impact of pain on patients, their families and communities is largely absent in most federal research plans.[3,4]

Additional studies and a comprehensive pain research agenda are needed to:

- Understand the role of stereotypes and bias in doctor-patient interactions
- Improve training for healthcare providers
- Plan educational interventions for patients
- Understand the differences in patient behaviors that may contribute to pain care disparities
- Develop culturally sensitive pain assessment tools
- Raise consciousness about disparities in pain management and barriers to effective healthcare overall

WEB RESOURCES

CDC Office of Minority Health and Health Disparities
http://www.cdc.gov/omhd/

Cover the Uninsured: a Project of the Robert Wood Johnson Foundation
http://covertheuninsured.org/

American Pain Society: Racial and Ethnic Identifiers in Pain Management: The Importance to Research, Clinical Practice, and Public Health Policy
http://www.ampainsoc.org/advocacy/ethnoracial.htm

Agency for Healthcare Research and Quality: Addressing Racial and Ethnic Disparities in Health Care
http://www.ahrq.gov/research/disparit.htm
http://www.ahrq.gov/qual/nhdr03/nhdrsum03.htm

REFERENCES

1. *About Minority Health.* Retrieved October 12, 2008 from CDC Office of Minority Health. Web site: http://www.cdc.gov/omhd/AMH/AMH.htm
2. Bonham VL (2001). Race, Ethnicity, and Pain Treatment: Striving to Understand the Causes and Solutions to the Disparities in Pain Treatment. *Journal of Law, Medicine & Ethics,* 129:52.
3. Green CR. (2003). The Unequal Burden of Pain: Confronting Racial and Ethnic Disparities in Pain. *Pain Medicine,* 4(3):277-294.
4. Green C. (2006). Disparities in Pain: Ethical Issues. *Pain Medicine,* 7(6):530-533.
5. Todd KH, Ducharme J, Choiniere M, Crandall CS, Fosnocht D, Homel P, et al. (2007). Pain in the Emergency Department: Results of the Pain and Emergency Medicine Initiative (PEMI) Multicenter Study. *The Journal of Pain,* 8(6):460-466.
6. Todd KH, et al. (1994) The effect of ethnicity on physician estimates of pain severity in patients with isolated extremity trauma. *JAMA,* 271(12):925-28.
7. Todd, Samaroo, Hoffman, et al. (1993) Ethnicity as a risk factor for inadequate emergency department analgesia. *JAMA,* 269(12):1537-39.
8. Paulson MR, Dekker AH, Aguilar-Gaxiola S. (2007). Eliminating Disparities in Pain Management. *J Am Osteopath Assoc,* 107(suppl_5), ES17-20.
9. Freeman HP, Payne R. (2000) Racial injustices in health care. *New Engl J Med,* 342(14):1045-1047.
10. Todd KH, Deaton C, D'Adamo AP, Goe L. (2000) Ethnicity and analgesic practice. *Ann Emerg Med,* 35(1):11-16.
11. Karpman, et al. (1997) Analgesia for emergency centers' orthopaedic patients: does an ethnic bias exist?, *Clinical Orthopaedics and Related Research,* 334:270-5.
12. Morrison R, et al. (2000) "We don't carry that" – Failure of pharmacies in predominantly nonwhite neighborhoods to stock opioid analgesics. *N Engl J Med,* 342:1023-1026.
13. Cleeland CS, Gonin, R, Baez, L, Loehrer, P, & Pandya, KJ. (1997). Pain and Treatment of Pain in Minority Patients with Cancer: The Eastern Cooperative Oncology Group Minority Outpatient Pain Study. *Ann Intern Med,* 127(9):813-816.
14. *Pain: Hope through Research.* Retrieved October 12, 2008 from National Institute of Neurological Disorders and Stroke (NINDS). Web site: http://www.ninds.nih.gov/disorders/chronic_pain/detail_chronic_pain.htm
15. Dalton J. (1998). A call for standardizing the clinical rating of pain intensity using a 0 to 10 rating scale. *Cancer Nursing,* 21(11):46–49.
16. Lebovits A. (2005) The ethical implications of racial disparities in pain: Are some of us more equal? *Pain Med,* 6:3-4.
17. Payne R, et al. (2002) Quality of Life Concerns in Patients with Breast Cancer. *Cancer,* 97:311-317.
18. Ng, Dimsdale, Shragg, et al. (1996) Ethnic differences in analgesic consumption for postoperative pain. *Psychosomatic Medicine,* 58:125-9.
19. *Racial and Ethnic Identifiers in Pain Management: The Importance to Research, Clinical Practice, and Public Health Policy: A Position Statement from the American Pain Society.* Approved by the APS Board of Directors, October 22, 2004. Retrieved October 12, 2008 from American Pain Society. Web site: http://www.ampainsoc.org/advocacy/ethnoracial.htm
20. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare* (2002). Retrieved October 10, 2008 from Institute of Medicine. Web site: http://www.iom.edu/?id=16740

Topic Brief

CHRONIC PAIN AND OPIOID TREATMENT

Effective management of chronic pain often requires a step-wise trial of different treatment options, a team of healthcare providers and social support from family and friends. Healthcare providers may start with behavioral and non-pharmacological interventions (e.g., hot/cold therapy, physical therapy, relaxation techniques) when devising pain treatment plans. However, pain relievers, including prescription pain medicines (opioid analgesics), are often prescribed to help alleviate pain and improve function.

Key Issues

- More than 76.5 million Americans suffer with pain.[1] The consequences of unmanaged chronic pain are devastating for patients. It is not uncommon for patients with intractable, debilitating pain—many of whom are often made to feel that the pain is "just in their heads"—to want to give up rather than living one more day in excruciating pain.
- For many patients, opioids are an integral part of a comprehensive pain management plan to help relieve pain, restore functioning and improve quality of life.[2,3]
- Unfortunately, patient access to these medications may be hindered by unbalanced state policies, persisting social stigma surrounding their use, as well as therapeutic switching and/or step therapies imposed by insurance companies.
- Unless a patient has a past or current personal or family history of substance abuse, the likelihood of addiction is low when opioids are taken as prescribed and under the guidance of a physician; however, they have the potential for misuse, abuse and diversion.
- Rising rates of prescription drug abuse and emergency room admissions related to prescription drug abuse, as well as an increase in the theft and illegal resale of prescription drugs, indicate that drug diversion is a growing problem nationwide.[4] The main source of drug diversion is unlikely the prescriber as was once assumed, but rather from theft by family, friends and workers in the home or from the sharing and selling of medications though often with good intentions.[5]
- Diverse players (e.g., lawmakers, educators, healthcare providers, the pharmaceutical industry, caregivers) must come together to address the dual public health crises of the undertreatment of pain and rising prescription drug abuse.[6]
- Alleviating pain remains a medical imperative—one that must be balanced with measures to address rising non-medical use of prescription drugs and to protect the public health.[6]

Opioids 101

Opioids include morphine, oxycodone, oxymorphone, hydrocodone, hydromorphone, methadone, codeine and fentanyl. Opioids are classified in several ways, most commonly based on their origin and duration of effects.[7]

Common classifications for opioids[7,8]

SOURCE	**Natural or semisynthetic:** Contained in or slightly modified (semisynthetic) from chemicals found in poppy resin	Synthetic: Synthesized in the laboratory
DURATION OF RESPONSE	**Short-acting:** Provide quick-acting pain relief and are used primarily as "rescue medication," as in acute pain	Long-acting: Provide longer duration of pain relief and are most often used for stable, chronic pain

One of the advantages of opioids is that they can be given in so many different ways. For example, they can be administered by mouth, rectal suppository, intravenous injection (IV), subcutaneously (under the skin), transdermally (in the form of a patch) or into a region around the spinal cord. Patches, IV injections and infusions are very important for patients who cannot swallow, or whose GI tracts are not working normally.[9]

Opioids are believed to work by binding to specific proteins (opioid receptors), which are found in specialized pain-controlling regions of the brain and spinal cord. When these compounds attach to certain opioid receptors, the electrical and chemical signals in these regions are altered, ultimately reducing pain.[7]

Because of their long history of use, the clinical profile of opioids has been very well characterized. Multiple clinical studies have shown that long-acting opioids, in particular, are effective in improving:

- Daily function
- Psychological health
- Overall health-related quality of life for patients with chronic pain[10]

However, some types of pain, such as pain caused by nerve compression or destruction, do not appear to be relieved by opioids.[8]

Adverse Effects

Side effects of opioids result primarily from activation of opioid receptors outside and within the nervous system. Activation of opioid receptors in the gut, for example, may cause constipation, nausea and vomiting, and other gastrointestinal effects. Tolerance to nausea and vomiting usually develops within the first few days or weeks of therapy, but some patients are intolerant to opioids and experience severe adverse side effects.[8] Other side effects include drowsiness, mental clouding and, in some people, euphoria.[7] Recent research shows that genetic variations may influence opioid metabolism.

Depending on the amount taken, opioids can depress breathing. The risk of sedation and respiratory depression is heightened when opioids are taken with other sedating medications (e.g., antihistamines, benzodiazepines), reinforcing the need to carefully monitor patients. However, this effect is usually is not present after a patient has taken opioids regularly.

Careful Monitoring of and Open Communication with Patients

Patients taking opioids must be carefully selected and monitored, and should speak openly with their healthcare provider about noticeable improvements in functioning, as well as side effects and other concerns (e.g., constipation, fears of addiction).

The Four "A's"

Analgesia – Is the pain relief clinically significant? Is there a reduction in the pain score (0-10)?

Activity levels – What is the patient's level of physical and psychosocial functioning? Has treatment made an improvement?

Adverse effects – Is the patient experiencing side effects from pain relievers? If so, are they tolerable?

Aberrant behaviors – Are there any behaviors of concern such as early refills or lost medication? Does the patient show signs of misuse, abuse or addiction? What is the plan of action?

Source: Passik & Weinreb, 1998; Passik & Portenoy, 1998

The American Pain Foundation's *Target Chronic Pain* materials help facilitate open dialogue between patients and their healthcare team, and give prescribers tools for selecting, monitoring and following patients. To access these resources, visit www.painfoundation.org and click on the Publications tab.

Dual Public Health Crises: Balancing Medical Imperative to Relieve Suffering and Protect Public Safety

Pain affects more Americans than diabetes, heart disease and cancer combined, and it is one of the leading causes of disability in the United States. Recognition of pain as a growing public health crisis has led to the establishment of specialized pain clinics, treatment guidelines for certain types of pain, as well as greater use of treatment strategies to effectively alleviate pain and improve functioning, including prescription pain medicines.

As the therapeutic use of opioids has increased to appropriately address pain, there has been a simultaneous and dramatic rise in non-medical use of prescription drugs.[11] When abused—that is, taken by someone other than the patient for whom the medication was prescribed, or taken in a manner or dosage other than what was prescribed—prescription medications can produce serious adverse health effects and can lead to addiction, overdose and even death.

People who abuse opioids typically do so for the euphoric effects (e.g., the "high"); however, most abusers are ***not*** patients who take opioids to manage pain.[12] Rather, they are often people within the social network of the patient. In fact, 71% of people abusing prescription pain relievers received them from a friend or family member without a prescription.[5] Prescription pain relievers are usually stolen from medicine cabinets, purchased or shared in schools, or simply given away.

Picture of Prescription Drug Abuse in America

- An estimated 2.2 million Americans abused pain medications for the first time in 2006.[12] The rate of new abuse of opioids has risen most dramatically among teenagers.
- Between 1992 and 2002, reported abuse by teenagers increased by 542%.[13]
- From 1999 to 2004, unintentional poisoning deaths associated with opioids and hallucinogens rose by 55%, and the increase has been attributable primarily to prescription pain relievers.[14]
- According to 2005 and 2006 National Surveys on Drug Use and Health, an annual national average of 6.2% of persons aged 12 or older had used a prescription psychotherapeutic drug non-medically in the 12 months leading up to the survey; an average of 9.1% of youths aged 12 to 17 were past year non-medical users of any prescription psychotherapeutic drug.[12]
- Nearly 600,000 emergency department visits involved non-medical use of prescription or over-the-counter (OTC) pharmaceuticals or dietary supplements. Opiates/opioid analgesics accounted for 33% of the non-medical visits. Anti-anxiety agents (sedatives and hypnotics) accounted for 34% of the non-medical visits.[4]

The growing prevalence of prescription drug abuse not only threatens the lives of abusers; concerns about misuse, abuse and diversion may also jeopardize effective pain management by impeding patient access to opioids. Fear of scrutiny by regulators or law enforcement, and specific action by some agencies, has had a "chilling effect" on the willingness of some doctors, nurse practitioners and physician assistants to prescribe opioids.[6,15]

Moreover, high profile reports of drug abuse, diversion and addiction, or of legal actions taken against prescribers have helped perpetuate a negative—and sometimes false—picture of chronic pain management.[6] Over time, these reports overshadow untold stories of people with pain—those whose lives have been shattered by unrelenting pain—who get needed pain relief from these medications. Understanding the difference between tolerance, physical dependence, abuse and addiction is also critical to telling the story (See page 31-32 for definitions). According to medical experts, use of the term "narcotic" in news reports may further reinforce the myths and misconceptions of this class of drugs, given the negative connotation.[6]

"...[T]he attitude toward opioids has ranged from complete avoidance to widespread therapeutic use with minimal caution. These extremes have been driven by insufficient appreciation of risks by those at one end of the spectrum, and excessive fear of punitive regulatory scrutiny or exaggerated perceptions of addictive risk by those at the other. When opioids are prescribed for pain control in adequately evaluated, selected, and monitored patients, addiction is rare."

— Perry Fine, Topics in Pain Management

Strategies to Address Twin Public Health Crises

Systematic and targeted approaches are essential to address the growing prevalence and complexity of prescription drug abuse, while simultaneously ensuring that people with legitimate medical needs receive effective treatment.

These approaches can generally be categorized as follows:

- Legislative strategies to create balanced and consistent regulation and improve state-based prescription drug monitoring programs.
- Educational efforts to raise awareness about prescription drug abuse and its dangers among schools, families, healthcare providers, patients and potential abusers.
- Medical strategies to help identify and monitor patients who require opioid management, to include the incorporation of risk management into the treatment plan (e.g., treatment agreements, urine testing and monitoring, transition planning, collaborative practice with addiction medicine and behavioral health specialists).
- Pharmaceutical industry strategies to help prevent misuse, abuse and diversion by developing new tamper resistant packaging and/or formulations (e.g., tamper-resistant bottles, electromagnetic chips to track medication, new formulations that could resist or deter common methods of opioid abuse).

For additional recommendations, see the American Pain Foundation's report outlining critical barriers to appropriate opioid prescribing for pain management, *Provider Prescribing Patterns and Perceptions: Identifying Solutions to Build Consensus on Opioid Use in Pain Management.* This 16-page report calls for a more balanced perspective of the risks and benefits of these medications in practice and policy and summarizes key challenges and actionable solutions discussed by leading pain experts at a roundtable meeting hosted by APF.

Making the Grade: Evaluation of State Policies

The Pain & Policy Studies Group (PPSG) report "Achieving Balance in State Pain Policy: A Progress Report" graded states on quality of its policies affecting pain treatment and centered on the balance between preventing abuse, trafficking and diversion of controlled substances and simultaneously ensuring the availability of these medications for legitimate medical purposes. PPSG researchers evaluated whether state pain policies and regulations enhance or impede pain management and assigned each state a grade from 'A' to 'F.'

State Grades for 2008

State	2008 Grade	State	2008 Grade
Alabama	B+	Montana	C+
Alaska	C+	Nebraska	B+
Arizona	B+	Nevada	C
Arkansas	B	New Hampshire	B
California	B	New Jersey	C+
Colorado	B	New Mexico	B+
Connecticut	B	New York	C
Delaware	C+	North Carolina	B
District of Columbia	C+	North Dakota	B
Florida	B	Ohio	B
Georgia	B	Oklahoma	C+
Hawaii	B	Oregon	A
Idaho	B	Pennsylvania	C+
Illinois	C	Rhode Island	B+
Indiana	C+	South Carolina	C+
Iowa	B	South Dakota	B
Kansas	A	Tennessee	C
Kentucky	B	Texas	C
Louisiana	C	Utah	B+
Maine	B+	Vermont	B+
Maryland	B	Virginia	A
Massachusetts	B+	Washington	B+
Michigan	A	West Virginia	B
Minnesota	B+	Wisconsin	A
Mississippi	C+	Wyoming	C+
Missouri	C+		

Source: The Pain & Policy Studies Group, http://www.painpolicy.wisc.edu/Achieving_Balance/PRC2008.pdf.

At a Glance: Differentiating physical dependence, tolerance, abuse and addiction

Unfortunately, confusion between normal physiological responses to opioids (physical dependence and tolerance) and pathological phenomena such as addiction or abuse persist. Such misunderstandings not only reinforce the stigma surrounding legitimate medical use of these medicines, they also fuel fears of addiction and, in turn, may impinge on patient access to these medications. Although the use of opioids carries some risk of addiction, clinical studies have shown that the potential for addiction is low for the vast majority of patients using opioids for the long-term management of chronic pain.[17] As with any medication, there are risks, but these risks can be managed.

"Universal agreement on definitions of addiction, physical dependence and tolerance is critical to the optimization of pain treatment and the management of addictive disorders."

— Consensus document from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine

Physical dependence is characterized by biological changes that lead to withdrawal symptoms (e.g., sweating, rapid heart rate, nausea, diarrhea, goosebumps, anxiety) when a medication is discontinued, and is not related to addiction. Physical dependence differs from psychological dependence, or the cravings for the euphoria caused by opioid abuse. Symptoms of physical dependence can often be ameliorated by gradually decreasing the dose of medication during discontinuation.[7]

Tolerance is a biological process in which a patient requires increasing amounts of a medication to achieve the same amount of pain relief. Dose escalations of opioid therapies are sometimes necessary and reflect a biological adaptation to the medication. Although the exact mechanisms are unclear, current research indicates that tolerance to opioid therapy develops from changes in opioid receptors on the surface of cells.[7] Thus, the need for higher doses of medication is not necessarily indicative of addiction.[3]

Addiction is a disease characterized by preoccupation with and compulsive use of a substance, despite physical or psychological harm to the person or others.[3] Behaviors suggestive of addiction may include: taking multiple doses together, frequent reports of lost or stolen prescriptions, and/or altering oral formulations of opioids.

Abuse is the intentional self-administration of a medication for a non-medical purpose, such as to obtain a high.[3] Both the intended patient and others have the potential to abuse prescription drugs; in fact, the majority of people who abuse opioids do not suffer from chronic pain.[12]

Pseudo-addiction describes patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications and may otherwise seem inappropriately "drug seeking," which may be misidentified as addiction by the patient's physician. Pseudo-addiction can be distinguished from true addiction in that this behavior ceases when pain is effectively treated.[3]

MISUSE VS. ABUSE?

- **Medical Misuse:** Legitimate use of a valid personal prescription but using differently from provider's instruction, such as taking more frequently or higher than the recommended doses. Use may be unintentional and considered an educational issue.
- **Medical Abuse:** Valid personal prescription by using for reasons other than its intent, such as to alleviate emotional stress, sleep restoration/prevention, performance improvement, etc. Use may be unintentional and considered an educational issue.
- **Prescription Drug Misuse:** Intentional use of someone else's prescription medication for the purpose of alleviating symptoms that may be related to a health problem. The use may be appropriate to treat the problem but access to obtain this drug may be difficult/untimely or may have been provided from a well-intentioned family member or friend.
- **Prescription Drug Abuse:** Intentional use of a scheduled prescription medication to experiment, to get high or to create an altered state. Access to the source may be diversion from family, friends or obtained on the street. Inappropriate or alteration of drug delivery system, used in combination of other drugs or used to prevent withdrawal from other substances that are being abused are included in this definition.

Source: Carol J. Boyd PhD, MSN, RN, Director, Institute for Research on Women and Gender, Substance Abuse Research Center, University of Michigan

Risk factors for opioid misuse include, but are not limited to:[2,3,19]

- Personal or family history of prescription drug or alcohol abuse
- Cigarette smoking
- History of motor vehicle accidents
- Substance use disorder
- Major psychiatric disorder (e.g., bipolar disorder, major depression, personality disorder)
- Poor family support
- History of preadolescent sexual abuse

NOTE: Unless a patient has a past or current history of substance abuse, the potential for addiction is low when opioid medications are prescribed by a doctor and taken as directed. Those patients who suffer with chronic pain and addictive disease deserve the same quality of pain treatment as others, but may require greater resources in their care.

WEB RESOURCES

Opioid RX
http://pain-topics.org/opioid_rx/#RiskManage

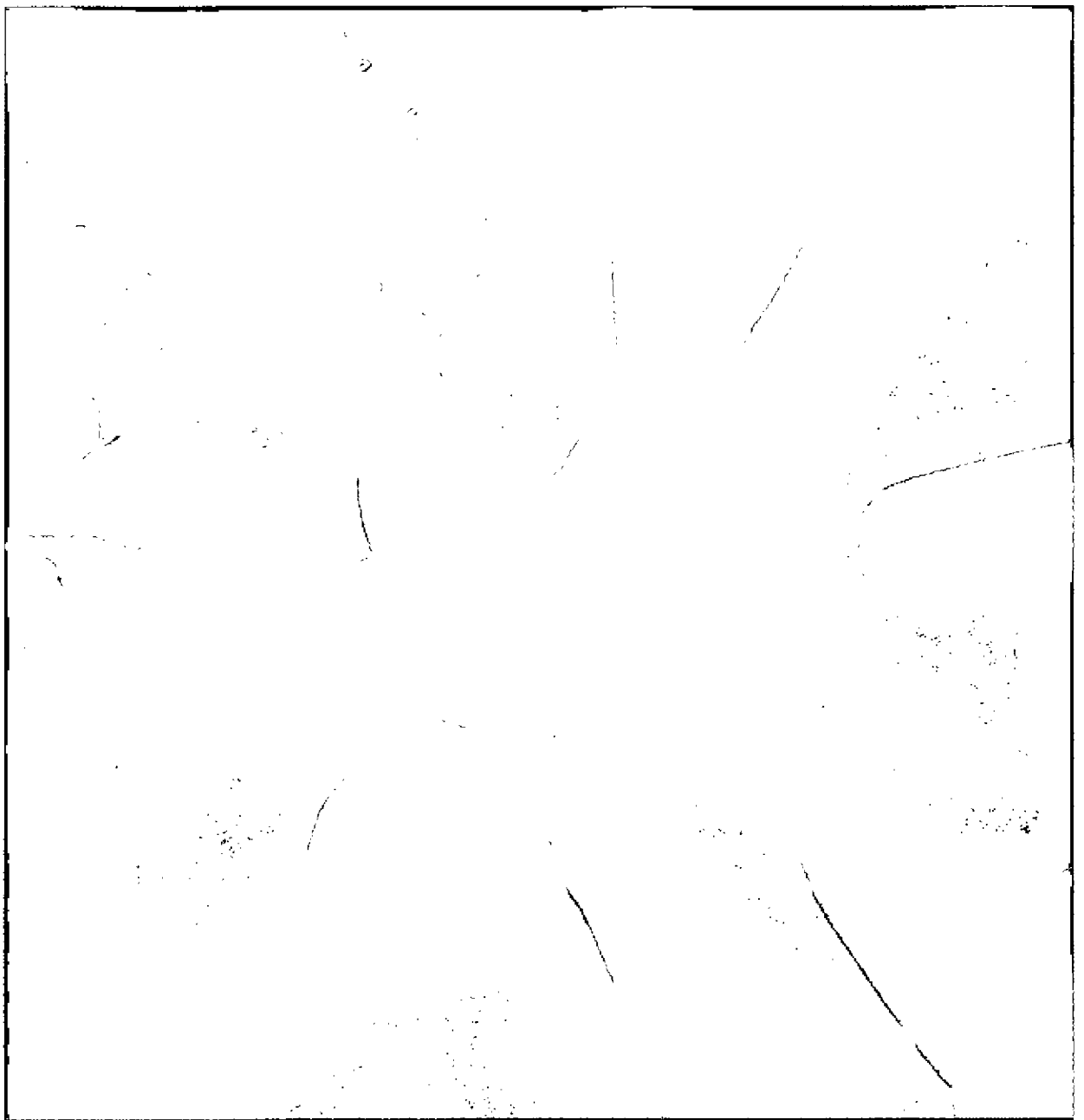
Tufts Health Care Institute Program on Opioid Risk Management
http://www.thci.org/opioid/

Opioid Risk Management PainEDU
http://www.painedu.org/soap.asp

Emerging Solutions
http://www.emergingsolutionsinpain.com/index.php?option=com_frontpage&Itemid=1

REFERENCES

1. National Center for Health Statistics. Health, United States, 2006 With Chartbook on Trends in the Health of Americans. Hyattsville, MD. Available at http://www.cdc.gov/nchs/data/hus/hus06.pdf.
2. Fine, PG. Opioid Therapy as a Component of Chronic Pain Management: Pain Experts Weigh In on Key Principles to Optimize Treatment. *Topics in Pain Management.* May 2008;23(10):1-8.
3. Katz NP, Adams EF, Chilcoat H, Colucci RD, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain.* 2007;23:648-660.
4. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Drug Abuse Warning Network, 2005: National Estimates of Drug-Related Emergency Department Visits. DAWN Series D-29, DHHS Publication No. (SMA) 07-4256, Rockville, MD, 2007. Available at http://dawninfo.samhsa.gov/files/DAWN-ED-2005-Web.pdf.
5. Substance Abuse and Mental Health Services Administration. (2008). *Results from the 2007 National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, NSDUH Series H-34, DHHS Publication No. SMA 08-4343). Rockville, MD. See http://oas.samhsa.gov/nsduh/2k7nsduh/2k7Results.pdf.
6. American Pain Foundation. Provider Prescribing Patterns and Perceptions: Identifying Solutions to Build Consensus on Opioid Use in Pain Management—A Roundtable Discussion. April 2008. Available at www.painfoundation.org.
7. Schumacher MA, Basbaum AI, Way WL. Opioid analgesics & antagonists. In: Katzung, ed. Basic and clinical pharmacology. 10th ed. New York, NY: McGraw Hill, 2007;489-502.
8. McQuay H. Opioids in pain management. *The Lancet.* 1999;353:2229-2232.
9. American Pain Foundation. Treatment Options: A Guide for People Living with Pain. 2007. Available at www.painfoundation.org.
10. Furlan AD, Sandoval JA, Mailis-Gagnon AM, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ.* 2006;11:1589-1594.
11. Kuehn BM. Opioid prescriptions soar: increase in legitimate use as well as abuse. *JAMA.* 2007;297:249-250.
12. Substance Abuse and Mental Health Services Administration. (2007). Results from the 2006 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-32, DHHS Publication No. SMA 07-4293). Rockville, MD.
13. Bollinger LC, Bush C, Califano JA, et al. Under the counter: the diversion and abuse of controlled prescription drugs in the U.S. The National Center on Addiction and Substance Abuse at Columbia University (CASA), July 2005.
14. Centers for Disease Control. Unintentional poisoning deaths – United States, 1999-2004. *MMWR.* February 9, 2007;56(05):93-96.
15. Lin JJ, Afandre D, Moore C. Physician attitudes toward opioid prescribing for patients with persistent noncancer pain. *Clin J Pain.* 2007;23:799-803.
16. Fine PG, Portenoy RK: Clinical Guide to Opioid Analgesia, 2nd Edition. New York: Vendome, 2007
17. Sinatra R. Opioid analgesics in primary care: challenges and new advances in the management of noncancer pain. *J Am Board Fam Med.* 2006;19:165-77.
18. Boyd C. Presentation at the NIDA/AMA Joint Meeting, Pain, Opioids, and Addiction: An Urgent Problem for Doctors and Patients, NIH, Bethesda, Maryland, March 5, 2007.



"The purpose of life…is to be useful, to be honorable, to be compassionate, to make some difference…"

—Ralph Waldo Emerson

Topic Brief

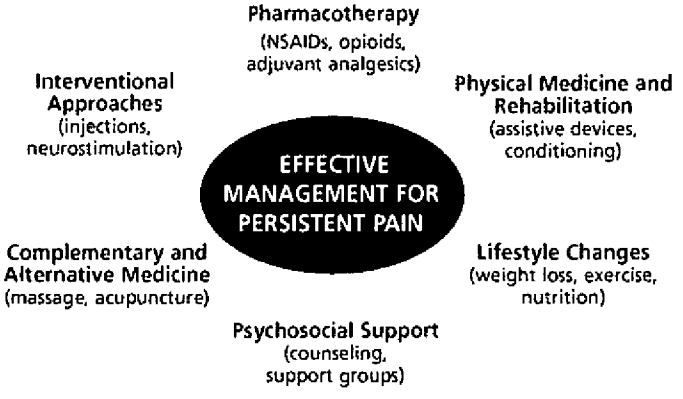
INTEGRATIVE MEDICINE: NON-DRUG TREATMENT OPTIONS FOR PAIN MANAGEMENT

Pain management continues to challenge healthcare providers and places added strain on an already fragmented health care system. The U.S. health system was built around acute illness; however, because of advances in modern medicine and increased longevity, many Americans are living longer and with one or more chronic conditions (for example, cancer, diabetes, heart disease and arthritis), which require careful coordination of care and symptom management.

While pain is a symptom of many chronic diseases and is expected after many surgical procedures, persistent pain should not be viewed simply as a symptom. According to experts, the pain itself becomes a disease when the origin of the pain signals fails to shut off due to damage of the pain alarm system, leaving the person with persisting pain.

Whatever the cause, chronic pain transcends the physical hurting. Persistent pain interferes with daily life and relationships, and takes a tremendous toll on a person's mind, body and spirit. It's no surprise that pain and associated problems (e.g., medication side effects, depression and anxiety, limited mobility) are best managed using a combination of treatments tailored to each patient. This is referred to as a "multi-modal" or integrative approach.

Multi-modal Therapeutic Strategies for Managing Pain and Related Disability



Integrative medicine combines conventional medicine with complementary healing techniques, such as massage, yoga and acupuncture, to address the specific needs. Because an interdisciplinary approach to pain management is patient-centered, patients learn how to manage and cope with pain by playing an active role in their treatment plan.

Integrative medicine combines treatments from conventional medicine and complementary and alternative therapies for which there is some high-quality evidence of safety and effectiveness.[1] Being able to deliver integrated medicine, which incorporates proven CAM therapies into "mainstream" care, is increasingly important to consumers and healthcare providers.[4]

Benefits of Combined Treatment Modalities

While medications remain an integral part of pain management plans, non-drug therapies may be used to supplement and enhance the effectiveness of current pain medications. These strategies also offer additional options for those patients at greater risk for, or who are intolerant of, medication side effects.

Moreover, a growing body of research reinforces the benefits of interventions that address the psychosocial aspects of pain, especially given recent evidence of a biological link between the regions of the brain involved with depression and pain regulation. People with pain often suffer from depression, which can affect a patient's thinking, concentration and behavior, and increase pain sensitivity and severity.

Effective pain management may also require lifestyle changes that are supportive of patient mobility and independence.[2] For example, to improve daily functioning, specific therapies may be suggested to increase muscle strength and flexibility, enhance sleep and reduce fatigue, and assist patients in performing usual activities and work-related tasks.

As with the management of other chronic illnesses, patients with chronic pain need to play an active role in their care and incorporate non-drug options and other lifestyle changes (e.g., exercise, proper nutrition) over the long-term.

Patients Seek Complementary Treatments

In their quest for better pain relief, patients are increasingly turning to non-drug approaches to help ease their discomfort and give them a sense of empowerment and control. There are a wide variety of non-drug therapies available to treat pain and related disability including:

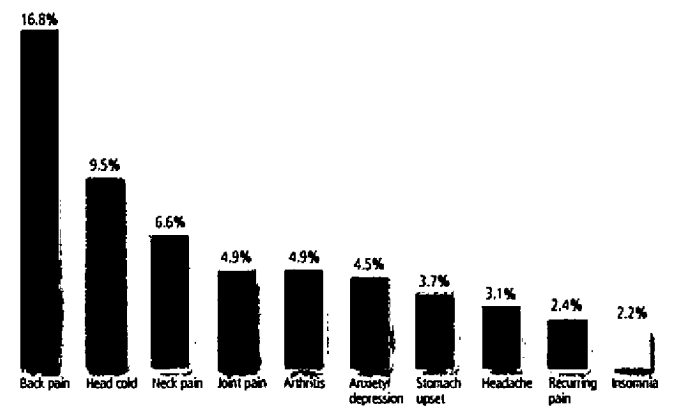
- *Psychosocial interventions* – cognitive behavioral therapy, stress management
- *Rehabilitation techniques* – exercise, heat or cold therapy, physical therapy
- *Complementary and alternative medicine* – meditation, acupuncture, hypnotherapy, yoga, aromatherapy, massage, touch therapy

Not surprisingly, pain conditions are among those most likely to prompt patients to turn to complementary and alternative medicine (CAM) therapies. These practices also give patients a greater sense of control, so they no longer feel that they are solely dependent on a single pill or procedure.

COMMON NON-DRUG OPTIONS FOR PAIN RELIEF

- Stress management techniques (e.g., meditation, deep breathing and relaxation exercises)
- Massage
- Application of heat or cold, including heating pads or ice packs
- Acupuncture
- Visualization
- Physical therapy, including stretching or exercise
- Hypnotherapy
- Psychological and spiritual counseling
- Biofeedback
- Transcutaneous electrical nerve stimulation, also known as TENS

Diseases/Conditions for Which CAM is Used Most Often



Source: NCCAM, *The Uses of CAM in the United States.*

What is CAM?

CAM includes a diverse group of healing systems, practices and products that are not part of conventional medicine. Examples of CAM therapies include acupuncture, massage, meditation, hypnosis, yoga and herbal therapies. These approaches are increasingly used to help manage pain and related issues (e.g., depression, anxiety, fatigue) and enhance patients' quality of life. NCCAM, one of 27 institutes and centers designated by the National Institutes of Health, is the lead agency for scientific research on CAM and groups these therapies into four areas.

CAM DOMAINS DEFINED	
Mind-body medicine	Uses a variety of techniques designed to enhance the mind's ability to affect the body's function and symptoms. Examples include meditation, hypnosis, guided imagery, prayer, as well as art or music therapy.
Biologically based practices	Use substances found in nature, such as herbs, special diets or vitamins. Some examples include dietary supplements or herbal products (e.g., garlic, ginger, Kava Kava).
Manipulative and body-based practices	Based on manipulation or movement of one or more parts of the body. Examples include massage and chiropractic or osteopathic manipulation.
Energy medicine	Involves the use of energy fields, such as magnetic fields or biofields (energy that some believe surround and run through the body). Examples include qi gong, Reiki and therapeutic touch.

Many CAM practices are gentle methods that tend to have fewer side effects, which is part of their appeal to patients. Patients also use these therapies to help alleviate the associated stress, depression and insomnia that can accompany and worsen pain sensations.

Some CAM practices, such as acupuncture, massage and chiropractic care require the practitioner to be licensed. It's important for patients to research and find a CAM practitioner who is certified, willing and equipped to coordinate with other members of the patient's health team, and has experience working with patients with chronic pain.

When tailored to the individual patient, non-drug approaches to pain management can help:

- Allow patients to take an active role in managing their pain, thereby, improving patient satisfaction
- Address the physical, emotional and spiritual needs of patients
- Reduce pain and manage related symptoms (e.g., pain and anxiety, depression, insomnia, fatigue)
- Enhance the effectiveness and minimize adverse effects of medications
- Reduce health care costs by reducing doctor visits and reliance on medications
- Improve functioning and the ability to perform activities of daily living
- Enhance wellness and quality of life

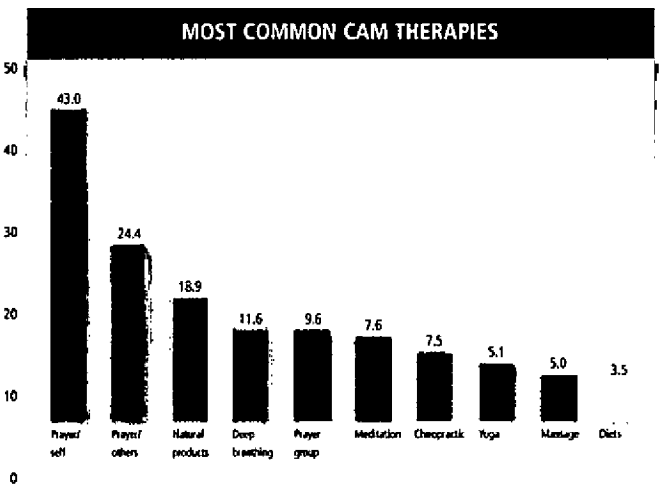
More and more Americans are turning to CAM to help manage and treat various health problems, including pain and distress.

- An estimated 36% of American adults use some form of CAM, and this percentage jumps to 62% if prayer for health reasons and megavitamin therapy are included.[3]
- Americans spend at least $34-47 billion on CAM therapies, exceeding out of pocket expenses for all U.S. hospitalizations. CAM is expected to grow by 15% each year.[3]
- People report using CAM because these methods mirror their personal beliefs, values and philosophical orientations toward life.[4]
- Many people use CAM to help relieve back pain, joint pain, severe headache and pain associated with migraines, dental and jaw pain and for a variety of other reasons.[4]

Barriers to Fully Integrating CAM

Despite CAM's growing popularity, there are barriers to its widespread use. According to CAM experts, these include:

- Limited scientific evidence about the safety and effectiveness of certain therapies. Studies are underway to research specific CAM practices for pain management.
- Lack of professional training in CAM and integrative medicine and limited resources to coordinate services.
- Restricted health insurance coverage. Many CAM therapies are not yet covered by health insurance carriers and are, therefore, only available to patients on an outpatient fee-for-service basis. Insurers tend to restrict reimbursement to "medically necessary" therapies and without the data to back up their effectiveness, these practices are not covered.



Source: Barnes P, Powell-Griner E, McFann K, Nahin R, CDC Advance Data Report #343, *Complementary and Alternative Medicine Use Among Adults*, United States, 2002. May 27, 2004.

- Lack of education (on the part of consumers and providers) about the appropriate use of CAM therapies and how best to integrate them with standard pain treatments.
- Misperceptions about CAM therapies as "elusive, nonsensical options."

Source: American Pain Foundation, *Pain Community News*, Spring 2008.

Paying for non-drug therapies

The majority of CAM treatments are not currently covered by traditional insurance plans, largely due to the absence of scientific evidence proving the effectiveness of some CAM therapies. When coverage for CAM is offered, it is generally limited to more common therapies such as acupuncture and massage. Most people must pay for CAM services out-of-pocket; however, consumer interest has prompted more insurance companies to consider CAM coverage.

A study in Washington State, where private health insurers are legally required to cover licensed CAM providers, found that a significant number of people were utilizing CAM insurance benefits with only a modest effect on insurance expenditures.[5]

Given the high cost and low insurance coverage of many CAM therapies, it is important that patients, especially those that are no longer able to work, have access to low cost, at-home therapies that provide effective pain relief. These may include heat and cold therapies, relaxation techniques and exercise.

People living with chronic pain are increasingly turning to CAM to help alleviate their suffering and improve their quality of life. The addition of these therapies often results in better pain relief and fewer side effects. However, more research is needed to prove the effectiveness of certain therapies and increase the likelihood that they will be covered by conventional insurance providers and offered as an option to all patients living with pain.

With nearly half of all consumers concerned about the safety of their health care,[6] the use of CAM and other non-drug treatments for pain management is expected to grow as non-drug therapies are proven safe and effective and adopted into routine health care.[7]

For a snapshot of recent research on select CAM therapies, see the Spring 2008 issue of *Pain Community News* at www.painfoundation.org.

REFERENCES

1. *What is CAM?* Retrieved October 10, 2008 from National Center for Complementary and Alternative Medicine (NCCAM). Web site: http://nccam.nih.gov/health/whatiscam/
2. Ahmad, M, Goucke, C.R. (2002) Management strategies for the treatment of neuropathic pain in the elderly. *Drugs Aging,* 19(12):929-4.
3. Barnes, P., Powell-Griner, E., McFann, K., Nahin, R. *CDC Advance Data Report* #343. Complementary and Alternative Medicine Use Among Adults: United States, 2002. May 27, 2004.
4. *Treatment Options: A Guide for People Living with Pain.* Retrieved October 10, 2008 from American Pain Foundation. Web site: http://www.painfoundation.org/Publications/TreatmentOptions2006.pdf
5. Lafferty, W.E., Tyree, P.T., et al. (2006) Insurance Coverage and Subsequent Utilization of Complementary and Alternative Medical (CAM) Providers. *Am J Manag Care,* 12(7):397–404.
6. Henry J. Kaiser Family Foundation (November 17, 2004). "Five years after IOM report on medical errors, nearly half of all consumers worry about the safety of their health care" Press release. Retrieved October 12, 2008 from http://www.kff.org/kaiserpolls/pomr111704nr.cfm
7. *The Pain Community News: Spring 2008,* 8(2). Retrieved October 10, 2008 from American Pain Foundation. Web site: http://www.painfoundation.org/Publications/PCN08spring.pdf

WEB RESOURCES

American Academy of Pain Management
www.aapainmanage.org

American Pain Foundation Treatment Options
www.painfoundation.org/Publications/TreatmentOptions2006.pdf

National Center for Complementary and Alternative Medicine (NCCAM)
www.nccam.nih.gov

The Office of Cancer Complementary and Alternative Medicine
www.cancer.gov/cam

Pain A to Z

Common Pain Terms and Syndromes

Hundreds of pain syndromes or disorders make up the spectrum of pain. There are the most benign, fleeting sensations of pain, such as a pin prick. There is the pain of childbirth, the pain of a heart attack, and the pain that sometimes follows amputation of a limb. There is also pain accompanying cancer and the pain that follows severe trauma, such as that associated with head and spinal cord injuries. A sampling of common pain terms and syndromes follows, listed alphabetically:

Acute Pain occurs suddenly due to illness, injury or surgery. It has a short duration that subsides when the injured tissue heals.

Arachnoiditis is a condition in which one of the three membranes covering the brain and spinal cord, called the arachnoid membrane, becomes inflamed. A number of causes, including infection or trauma, can result in inflammation of this membrane. Arachnoiditis can produce disabling, progressive, and even permanent pain.

Arthritis is the most prevalent cause of chronic disability in the United States. Millions of Americans suffer from arthritic conditions such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout. These disorders are characterized by joint pain in the extremities. Many other inflammatory diseases affect the body's soft tissues, including tendonitis and bursitis.

Back pain has become the high price paid by our modern lifestyle and is a startlingly common cause of disability for many Americans, including both active and inactive people. Common types of back pain include:

- **Sciatica** — back pain that spreads to the leg (see below).
- **Degenerative or ruptured disc** — type of back pain associated with the discs of the spine, the soft, spongy padding between the vertebrae (bones) that form the spine. Discs protect the spine by absorbing shock, but they tend to degenerate over time and may sometimes rupture.
- **Spondylolisthesis** — back condition that occurs when one vertebra extends over another, causing pressure on nerves and therefore pain.
- **Radiculopathy** — damage to nerve roots is a serious condition that can be extremely painful.

Treatment for a damaged disc includes drugs such as painkillers, muscle relaxants, and steroids; exercise or rest, depending on the patient's condition; adequate support, such as a brace or better mattress and physical therapy. In some cases, surgery may be required to remove the damaged portion of the disc and return it to its previous condition, especially when it is pressing a nerve root. Surgical procedures include discectomy, laminectomy, or spinal fusion. Minimally invasive procedures (vertebroplasty), certain complementary and alternative therapies and implantable devices may also help certain patients.

Breakthrough Pain is intermittent worsening of pain that occurs spontaneously or in relation to a specific activity. The pain increases above the level of pain being treated with ongoing analgesics (pain medications).

Burn pain can be profound and poses an extreme challenge to the medical community. First-degree burns are the least severe; with third-degree burns, the skin is lost. Depending on the injury, pain accompanying burns can be excruciating, and even after the wound has healed patients may have chronic pain at the burn site.

Cancer pain can accompany the growth of a tumor, the treatment of cancer, or chronic problems related to cancer's permanent effects on the body. Fortunately, most cancer pain can be treated to help minimize discomfort and stress to the patient.

Central pain syndrome — see Traumatic Pain below.

Chronic Pain is pain that persists for long periods of time (usually >3 months). Failure to treat acute pain promptly and appropriately at the time of injury, during initial medical and surgical care, and at the time of transition to community-based care, contributes to the development of chronic pain syndromes. In chronic pain, pain signals may remain active in the nervous system for weeks, months or even years. Chronic pain has no value or benefit; it is a disease of the nervous system.

Types of Chronic Pain:

- **Intermittent Pain** - episodic and may occur in waves or patterns.
- **Persistent Pain** - lasts 12 or more hours every day for more than three months.

Complex Regional Pain Syndrome, or CRPS, is a chronic pain condition that typically affects one or more limbs. It is accompanied by burning pain and hypersensitivity to temperature. Often triggered by trauma or nerve damage, CRPS causes the skin of the affected area to become characteristically shiny.

There are two types of CRPS:

- **CRPS I** (formerly known as Reflex Sympathetic Dystrophy Syndrome, or RSDS) is frequently triggered by tissue injury, but with no underlying or identifiable nerve injury.

- **CRPS II** (formerly known as Causalgia) is characterized by the same symptoms, but these cases are clearly associated with a specific nerve injury.

The cause of CRPS is not well understood, but experts believe it is due to a malfunction of the autonomic nervous system following blunt trauma to an arm or leg, after surgical procedures or even from minor injuries such as a sprain or fracture. Nerves begin to misfire, repeatedly sending pain impulses to the brain. The resulting pain seems out of proportion to the severity of the injury.

Deafferentation Pain: pain due to alteration or damage to the central nervous system (central pain or neuropathic pain) or may be alteration of nervous system within larger nerves or nerve roots before entry into central nervous system.

Fibromyalgia is a chronic pain disorder characterized by widespread musculoskeletal pain that has lasted for at least three months. People with fibromyalgia report general tenderness and soreness, muscle stiffness, especially in the morning, as well as fatigue. Stress or lack of sleep can make the symptoms of fibromyalgia worse. An estimated 6 million Americans have fibromyalgia, most of them women.

Headaches affect millions of Americans. The three most common types of chronic headache are migraines, cluster headaches, and tension headaches. Each comes with its own telltale brand of pain.

- **Migraines** are characterized by throbbing pain and sometimes by other symptoms, such as nausea and visual disturbances. Migraines are more frequent in women than men. Stress can trigger a migraine headache, and migraines can also put the sufferer at risk for stroke.
- **Cluster** headaches are characterized by excruciating, piercing pain on one side of the head; they occur more frequently in men than women.
- **Tension headaches** are often described as a tight band around the head.

Head and facial pain can be agonizing, whether it results from dental problems or from disorders such as cranial neuralgia, in which one of the nerves in the face, head, or neck is inflamed. Another condition, **trigeminal neuralgia** (also called tic douloureux), affects the largest of the cranial nerves and is characterized by a stabbing, shooting pain.

Muscle pain can range from an aching muscle, spasm, or strain, to the severe spasticity that accompanies paralysis. Another disabling syndrome is **fibromyalgia**, a disorder characterized by fatigue, stiffness, joint tenderness, and widespread muscle pain. **Polymyositis**, **dermatomyositis**, and **inclusion body myositis** are painful disorders characterized by muscle inflammation. They may be caused by infection or autoimmune dysfunction and are sometimes associated with connective tissue disorders, such as lupus and rheumatoid arthritis.

Myofascial pain syndromes affect sensitive areas known as trigger points, located within the body's muscles. Myofascial pain syndromes are sometimes misdiagnosed and can be debilitating.

Neuropathic Pain – is a type of pain that results from damage to or dysfunction of the nerves in either the peripheral or central nervous system, rather than stimulation of pain receptors (as is the case of somatic and visceral pain). Neuropathic pain can occur in any part of the body and is frequently described as a hot, burning sensation, which can be devastating to the affected individual. It can result from diseases that affect nerves (such as diabetes) or from trauma, or, because chemotherapy drugs can affect nerves, it can be a consequence of cancer treatment. Among the many neuropathic pain conditions are:

- **Diabetic neuropathy**, which results from nerve damage secondary to vascular problems that occur with diabetes;
- **Reflex sympathetic dystrophy syndrome** (see below), which can follow injury;
- **Phantom limb** and **post-amputation pain**, which can result from the surgical removal of a limb;
- **Postherpetic neuralgia**, which can occur after an outbreak of shingles; and
- **Central pain syndrome**, which can result from trauma to the brain or spinal cord.

Nociceptive pain - caused by an injury that stimulates pain receptors. Pain receptors, located on the tips of nerve cells, recognize and react to an unpleasant stimulus (pressure, extreme temperatures [hot or cold], substances released by other cells) and send pain signals through the nervous system for recognition and response. This type of pain may be accompanied by inflammation. Infections, burns, cuts, a severe lack of oxygen in the blood, and stretching of or pressure within an organ, can injure tissues and cause nociceptive pain.

Types of Nociceptive Pain:

- **Somatic Pain** - caused by injury to skin, muscles, bone, joint, and connective tissues. Deep somatic pain is usually described as dull or aching, and localized in one area. Somatic pain from injury to the skin or the tissues just below it often is sharper and may have a burning or pricking quality.
- **Visceral Pain** - originates from ongoing injury to the internal organs or the tissues that support them. When the injured tissue is a hollow structure, like the intestine or the gall bladder, the pain often is poorly localized and feels like cramping. When the injured structure is not a hollow organ, the pain may be pressure-like, deep, and stabbing.

Pain flares. Pain that suddenly erupts or emerges with or without an aggravating event or activity.

Peripheral Neuropathic Pain due to vascular disease or injury-such as vasculitis or inflammation of blood vessels, coronary artery disease, and circulatory problems-all have the potential to cause pain. Vascular pain affects millions of Americans and occurs when communication between blood vessels and nerves is interrupted. Ruptures, spasms, constriction, or obstruction of blood vessels, as well as a condition called ischemia in which blood supply to organs, tissues, or limbs is cut off, can also result in pain.

Reflex sympathetic dystrophy syndrome — see Complex Regional Pain Syndrome.

Repetitive stress injuries are muscular conditions that result from repeated motions performed in the course of normal work or other daily activities. They include:

- writer's cramp, which affects musicians and writers and others,
- compression or entrapment neuropathies, including carpal tunnel syndrome, caused by chronic overextension of the wrist and
- tendonitis or tenosynovitis, affecting one or more tendons.

Sciatica is a painful condition caused by pressure on the sciatic nerve, the main nerve that branches off the spinal cord and continues down into the thighs, legs, ankles, and feet. Sciatica is characterized by pain in the buttocks and can be caused by a number of factors. Exertion, obesity, and poor posture can all cause pressure on the sciatic nerve. One common cause of sciatica is a herniated disc.

Shingles and other painful disorders affect the skin. Pain is a common symptom of many skin disorders, even the most common rashes. One of the most vexing neurological disorders is shingles or herpes zoster, an infection that often causes agonizing pain resistant to treatment. Prompt treatment with antiviral agents is important to arrest the infection, which if prolonged can result in an associated condition known as **postherpetic neuralgia**. Other painful disorders affecting the skin include:

- **Vasculitis**, or inflammation of blood vessels;
- Other infections, including **herpes simplex**;
- Skin **tumors** and **cysts**, and

Tumors associated with **neurofibromatosis**, a neurogenetic disorder.

Somatic pain—see Nociceptive Pain.

Sports injuries are common. Sprains, strains, bruises, dislocations, and fractures are all well-known words in the language of sports. Pain is another. In extreme cases, sports injuries can take the form of costly and painful spinal cord and head injuries, which cause severe suffering and disability.

Spinal stenosis refers to a narrowing of the canal surrounding the spinal cord. The condition occurs naturally with aging. Spinal stenosis causes weakness in the legs and leg pain usually felt while the person is standing up and often relieved by sitting down.

Surgical pain may require regional or general anesthesia during the procedure and medications to control discomfort following the operation. Control of pain associated with surgery includes presurgical preparation and careful monitoring of the patient during and after the procedure.

Temporomandibular disorders are conditions in which the temporomandibular joint (the jaw) is damaged and/or the muscles used for chewing and talking become stressed, causing pain. The condition may be the result of a number of factors, such as an injury to the jaw or joint misalignment, and may give rise to a variety of symptoms, most commonly pain in the jaw, face, and/or neck muscles. Physicians reach a diagnosis by listening to the patient's description of the symptoms and by performing a simple examination of the facial muscles and the temporomandibular joint.

Traumatic pain can occur after injuries in the home, at the workplace, during sports activities, or on the road. Any of these injuries can result in severe disability and pain. Some patients who have had an injury to the spinal cord experience intense pain ranging from tingling to burning and, commonly, both. Such patients are sensitive to hot and cold temperatures and touch. For these individuals, a touch can be perceived as intense burning, indicating abnormal signals relayed to and from the brain. This condition is called **central pain syndrome** or, if the damage is in the thalamus (the brain's center for processing bodily sensations), **thalamic pain syndrome**. It affects as many as 100,000 Americans with multiple sclerosis, Parkinson's disease, amputated limbs, spinal cord injuries, and stroke. Their pain is severe and is extremely difficult to treat effectively. A variety of medications, including analgesics, antidepressants, anticonvulsants, and electrical stimulation, are options available to central pain patients.

Visceral pain – see Nociceptive Pain.

Sources:

American Pain Foundation. *Treatment Options: A Guide for People Living with Pain*. Available at www.painfoundation.org.

"Pain: Hope Through Research," National Institutes of Neurological Disorders and Stroke. Publication date December 2001. NIH Publication No. 01-2406 . Last updated July 31, 2008.

Pain Resources

American Pain Foundation
A United Voice of Hope and Power over Pain

American Pain Foundation
888-615-7246
www.painfoundation.org

Key Publications

- *Pain Community News*, APF's quarterly newsletter
- *Pain Monitor*, APF's monthly e-news update
- *Treatment Options: A Guide for People Living with Pain*
- *Pain Resource Guide: Getting the Help You Need*
- *Targeting Chronic Pain Notebook* and companion provider resources
- APF Report, *Provider Prescribing Patterns and Perceptions: Identifying Solutions to Build Consensus on Opioid Use in Pain Management*
- Fact sheets on cancer pain, shingles/PHN, fibromyalgia, military/veterans and pain, among others
- Top 10 Tips Series, including:
  - Finding Quality Health Information Online
  - Exercising for Pain Relief
  - Making the Most of Your Medical Visits
  - Easing Pain Around the Holidays
  - Pain-free Tips for Travelers
  - Helpful Hints on the Road to Pain Relief
- Pain Care Bill of Rights

Special Projects/Initiatives

- APF's grassroots **Power Over Pain Action Network** (POPAN) has 72 POPAN leaders in 36 states tirelessly working to help improve pain care, legislation related to pain care, healthcare access and medical practices.
- **Military and Veterans Pain Initiative**
- **Spotlight Series** on cancer pain, fibromyalgia and shingles
- **Pain & Creativity**
- **Yoga for Chronic Pain**
- ***Let's Talk Pain*** Coalition, www.letstalkpain.org, launched in partnership with the American Academy of Pain Management and the American Society for Pain Management Nursing

For more information about APF's programs and services, see the 2007 Annual Report at http://www.painfoundation.org/About/2007AnnualReport.pdf

To subscribe to print or online publications, please visit www.painfoundation.org, or call Tina Register, Communications Manager, at (443) 690-4707 or tregister@painfoundation.org

Other Consumer Pain Associations

American Chronic Pain Association
800-533-3231
www.theacpa.org

National Pain Foundation
303-783-8899
www.nationalpainfoundation.org

Condition-Specific Pain Organizations

The American Pain Foundation keeps an updated and searchable listing of condition-specific patient advocacy and professional organizations at www.painfoundation.org. These include such groups as the Amputee Coalition of America, Arthritis Foundation, the National Vulvodynia Association, National Fibromyalgia Association and the American Diabetes Association, among others.

Professional Pain Associations

Alliance of State Pain Initiatives
608-262-0978
E-mail: aspi@mailplus.wisc.edu

American Academy Hospice and Palliative Medicine
847-375-4712
www.aahpm.org

American Academy of Pain Management
209-533-9744
www.aapainmanage.org

American Academy of Pain Medicine
847-375-4731
www.painmed.org

American Pain Society
847-375-4715
www.ampainsoc.org

American Society of Addiction Medicine
301-656-3920
www.asam.org

American Society for Pain Management Nursing
913-895-4606
www.aspmn.org

National Hospice & Palliative Care Organization
703-837-1500
www.nhpco.org

Other organizations

Pain Policy Studies

Pain and Policy Studies Group (PPSG)
608-263-7662
www.painpolicy.wisc.edu

Pain Law Studies

Pain and the Law
617-262-4990
www.painandthelaw.org

The Legal Side of Pain
865-560-1945
www.legalsideofpain.com

National Association of Attorneys General
www.naag.org

Drug Abuse/Addiction Groups

National Institute on Drug Abuse
301-443-1124
www.nida.nih.gov

Drug Enforcement Administration
Office of Diversion Control
800-882-9539
www.deadiversion.usdoj.gov

Partnership for a Drug-Free America
212-922-1560
http://drugfreeamerica.com

Substance Abuse and Mental Health Services Administration (SAMHSA)
877-726-4727
www.samhsa.gov

White House Office of National Drug Control Policy
800-666-3332
www.whitehousedrugpolicy.gov

Others

Center for Practical Bioethics
800-344-3829
www.practicalbioethics.org

Federation of State Medical Boards (FSMB)
817-868-4000
www.fsmb.org

National Family Caregivers Association
301-942-6430
www.nfcacares.org

"Pain is inevitable. Suffering is optional."

—Anonymous

American Pain Foundation
A United Voice of Hope and Power over Pain

201 N. Charles St., Suite 710 • Baltimore, MD 21201-4111 • 1-888-615-PAIN (7246)
info@painfoundation.org • www.painfoundation.org

The American Pain Foundation is solely responsible for the content and maintains editorial control of all materials and publications we produce. We gratefully acknowledge those who support our work. This publication was underwritten by support from Alpharma Pharmaceuticals LLC.

Publication date: October 2008

EXHIBIT F

Pain Medicine 2014; 15: 1911–1929
Wiley Periodicals, Inc.

Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients

Barbara Zedler, MD,* Lin Xie, MS,† Li Wang, PhD,† Andrew Joyce, PhD,* Catherine Vick, MS,* Furaha Kariburyo, MPH,† Pradeep Rajan, ScD,* Onur Baser, PhD,† and Lenn Murrelle, PhD, MSPH*

*Venebio Group, Richmond, Virginia; †STATinMED Research, Dallas, Texas, USA

Reprint requests to: Barbara K. Zedler, MD, Venebio Group, LLC, 7400 Beaufont Springs Drive, Suite 300, Richmond, VA 23225, USA.
Tel: 877-344-4347, ext. 507; Fax: 804-272-3497; E-mail: barb.zedler@venebio.com.

Disclosure: This research was funded by kaléo, Inc. The study was conceived, designed, executed, and reported by the authors who had sole control over the data and the decision to publish. Kaléo, Inc. reviewed and commented on the methods developed by the authors and reviewed the final manuscript for proprietary information. Drs. Murrelle, Zedler, Joyce, and Rajan are Principals of Venebio Group, LLC, which has research and consulting agreements with kaléo, Inc. and Reckitt-Benckiser Pharmaceuticals, Inc. and reports no additional conflicts of interest. The other coauthors report no conflicts of interest.

Abstract

Objective. Prescription opioid use and deaths related to serious toxicity, including overdose, have increased dramatically in the United States since 1999. However, factors associated with serious opioid-related respiratory or central nervous system (CNS) depression or overdose in medical users are not well characterized. The objective of this study was to examine the factors associated with serious toxicity in medical users of prescription opioids.

Design. Retrospective, nested, case-control analysis of Veterans Health Administration (VHA) medical, pharmacy, and health care resource utilization administrative data.

Subjects. Patients dispensed an opioid by VHA between October 1, 2010 and September 30, 2012 (N = 8,987).

Methods. Cases (N = 817) experienced life-threatening opioid-related respiratory/CNS depression or overdose. Ten controls were randomly assigned to each case (N = 8,170). Logistic regression was used to examine associations with the outcome.

Results. The strongest associations were maximum prescribed daily morphine equivalent dose (MED) ≥ 100 mg (odds ratio [OR] = 4.1, 95% confidence interval [CI], 2.6–6.5), history of opioid dependence (OR = 3.9, 95% CI, 2.6–5.8), and hospitalization during the 6 months before the serious toxicity or overdose event (OR = 2.9, 95% CI, 2.3–3.6). Liver disease, extended-release or long-acting opioids, and daily MED of 20 mg or more were also significantly associated.

Conclusions. Substantial risk for serious opioid-related toxicity and overdose exists at even relatively low maximum prescribed daily MED, especially in patients already vulnerable due to underlying demographic factors, comorbid conditions, and concomitant use of CNS depressant medications or substances. Screening patients for risk, providing education, and coprescribing naloxone for those at elevated risk may be effective at reducing serious opioid-related respiratory/CNS depression and overdose in medical users of prescription opioids.

Key Words. Prescription; Opioid; Toxicity; Overdose; Risk; Predictors

Introduction

Serious toxicity, including overdose, related to prescription opioid analgesics has increased dramatically in the United States since 1999 [1,2]. Opioids are central nervous system (CNS) depressants. Life-threatening opioid toxicity includes profound sedation/coma and severe respiratory depression that can result in death from respiratory arrest [3–5]. Prescription drug "overdose" is a type of serious toxicity in which the drug is used in amounts that exceed the individual's ability to tolerate the exposure, resulting in serious adverse effects. Serious opioid-related respiratory/CNS depression can occur unintentionally in patients using them for approved therapeutic indications ("medical users") and even at dosages in the recommended prescribing range. Medical users taking opioids as prescribed may experience circumstances that predispose them to opioid accumulation, prolonged duration of action or enhanced CNS, and consequent respiratory depression. Examples include certain comorbid conditions (e.g., impaired renal, hepatic, or respiratory function) and concomitant medications or substances (e.g., sedatives, alcohol). Opioid pain relievers were involved in nearly 17,000 deaths in 2010, representing a threefold increase since 1999 and three-fourths of all prescription drug poisoning deaths [1,2]. The alarming upward trajectory of fatal unintentional overdoses parallels increases of 29–80% in the use of prescription opioids for long-term management of chronic noncancer pain (2000–2005) in an estimated 9 million US adults per year currently [6–11]. Approximately 60% of overdoses occur in medical users of maximum prescribed daily morphine equivalent doses (MED) of 100 mg or more[1] or those who misuse opioid analgesics, typically prescribed by a single physician, to manage chronic pain [7]. The remaining 40% of overdoses occur in nonmedical users who abuse prescription opioids for recreational purposes, tend to receive prescriptions from multiple prescribers, and engage in diversion of prescription opioids to and from others [7,12,13].

The factors associated with *fatal* opioid-related overdose have been well characterized [2,7,12,14–21]. Patient-related factors include certain demographic characteristics and clinical comorbidities. Men have a higher opioid-related overdose death rate [12], but the percentage rise in deaths since 1999 is greater in women [15]. For prescription opioids, overdose death rates are highest in persons aged 45–54 years; non-Hispanic whites, American Indians and Alaskan Natives; rural and impoverished areas; and in the West and Southwest United States and the Appalachian states of Kentucky and West Virginia where the opioid analgesic prescribing rates are highest [2,8,12,18,19,22,23]. Geographic variations in overdose deaths reflect, in part, variations in opioid analgesic prescribing patterns, the number of physicians available, and state-regulated pain management policies rather than inherent patient differences [2,24]. Persons with a history of substance abuse, previous overdose, mental illness, and respiratory disease are significantly more likely to die of an opioid-related overdose [7,16,20,21,25,26]. Prescription drug-related factors significantly associated with fatal opioid-related overdose or serious toxicity include use of oxycodone, methadone, and extended-release formulations [7,12,16,18,27–29]; maximum prescribed daily MED exceeding 50 mg [21,25]; and concurrent use of other psychoactive CNS depressants (e.g., sedative–hypnotics, anxiolytics, alcohol) [1,20,26,30].

To date, most research on predictors of serious opioid-related toxicity or overdose has focused on fatal events, illicit opioids, nonmedical users of prescription opioids, or limited samples of medical users and used relatively small, geographically limited convenience samples. The objective of this study was to identify the factors independently most associated with overdose or life-threatening respiratory/CNS depression, including nonfatal events, among medical users of prescription opioids in a large, national, administrative health care database.

Methods

Study Design

A nested case-control design was used to examine factors associated with a diagnosis of serious opioid-related respiratory/CNS depression or overdose among Veterans Health Administration (VHA) patients who were dispensed an opioid by VHA. The study was exempt from Institutional Review Board review.

Study Setting and Data Source

A retrospective analysis of deidentified national administrative health care data was conducted using VHA Medical SAS datasets from October 1, 2010 through September 30, 2012. These datasets contain data for VHA-provided health care that is utilized primarily by US military veterans and a small number of nonveterans (e.g., employees, eligible family members, research participants) and include inpatient, outpatient, laboratory, radiology, pharmacy, vital signs, vital status, and enrollment information.

Study Sample

Study "cases" were defined as patients who satisfied the following criteria at any time between October 1, 2010 and September 30, 2012 (the "study period"): 1) were dispensed at least one opioid prescription by VHA (see Appendix I), identified by national drug code; and 2) had a claim for a serious opioid-related toxicity or overdose event based on International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes and Current Procedure Terminology (CPT) codes (Table 1) [7,21,31]. A serious opioid-related toxicity or overdose event was defined as follows: 1) a listed CNS or respiratory adverse effect code in addition to a listed poisoning event or external cause code occurring within ±1 day of

[1]Maximum prescribed daily morphine equivalent doses exceeding 200 mg are considered 'high-dose.' [55]

Table 1 Diagnostic codes for serious opioid-related toxicity including overdose

ICD-9-CM Diagnosis Codes	Description
Poisoning codes	
965.00	Poisoning by opium (alkaloids), unspecified
965.01	Poisoning by heroin
965.02	Poisoning by methadone
965.09	Poisoning by other opiates and related narcotic
Adverse effect codes	
518.81	Acute respiratory failure
518.82	Other pulmonary insufficiency, not elsewhere classified
780.0	Alteration of consciousness
786.03	Apnea
799.0	Asphyxia and hypoxemia
CPT codes for mechanical ventilation or critical care	
31500	Intubation, endotracheal, emergency procedure
94002	Ventilation assist and management, initiation of pressure, or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, each subsequent day
94660	CPAP ventilation; initiation and management
94662	CNAP ventilation; initiation and management
99291	Critical care, evaluation, and management of the critically ill or critically injured patient, first 30–74 minutes
External cause codes	
E850.0	Accidental poisoning by heroin
E850.1	Accidental poisoning by methadone
E850.2	Accidental poisoning by other opiates and related narcotics
E935.0	Adverse effects of heroin
E935.1	Adverse effects of methadone
E935.2	Adverse effects of other opioids and related narcotics

CNAP = continuous negative airway pressure; CPAP = continuous positive airway pressure; ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification.

the adverse effect; or 2) use of mechanical ventilation or critical care in addition to a listed poisoning event or external cause code occurring within ±1 day of the critical respiratory support. The first identified occurrence of opioid-related overdose or life-threatening respiratory/CNS depression ("index event") during the study period served as the "index date" for cases. All patients were required to have nonmissing age, sex, and race values in addition to continuous medical and pharmacy benefits in the 6 months before the index date (the "baseline period"). For cases, the follow-up period was calculated as the number of days after the end of the event until death, disenrollment, or the end of the study period.

For each case, 10 control patients were randomly selected and assigned from those who 1) were dispensed an opioid by VHA during the study period; 2) did not experience serious opioid-related toxicity or overdose as defined in the study; and 3) had complete data for age, sex, and race. The case index date was assigned to each of the 10 control patients, and the follow-up period for these controls was the number of days thereafter until death, disenrollment, or the end of the study period.

Baseline Variables

Baseline demographic variables included age group (18–34, 35–44, 45–54, 55–64, 65+ years), sex, race, marital status, body mass index, and the US Census region of the patient's VHA treatment center (Northeast, North Central, South, West, other). Baseline comorbidity measures included the Charlson Comorbidity Index score, calculated as the sum of assigned comorbidity category weights [32].

Other selected baseline comorbidities were stratified as pain-related and nonpain-related [33–36]. Pain-related comorbid conditions included low back disorders, other back/neck disorders, neuropathic disorders, fibromyalgia, headache/migraine, burns, traumatic injury, and motor vehicle accidents. Nonpain-related comorbidities included psychoactive substance use disorders including substance abuse and nonopioid substance dependence, tobacco use disorder, post-traumatic stress disorder, bipolar disorder, attention deficit hyperactivity disorder, schizophrenia, anxiety disorder, obsessive-compulsive–disorder, cardiovascular disease, endocarditis, viral and alcoholic hepatitis), pancreatitis, sexually transmitted

disease, herpes simplex infection, skin infections/abscesses, sleep apnea, and obesity.

Additional baseline variables included the number of opioid prescriptions dispensed by VHA, opioid used (categorized by active ingredient, formulation [extended-release/long-acting vs short-acting], and route [oral, parenteral, transdermal, other]), and the maximum prescribed daily MED. For each opioid prescription dispensed during the baseline period, the product of the number of units dispensed and the opioid strength per unit (milligrams) was divided by the number of days supplied. The resulting opioid daily dose dispensed (milligrams per day) was then multiplied by a conversion factor derived from published sources to estimate the daily dose in morphine equivalents (MED) (see Table 2) [37–42]. The maximum prescribed daily MED during the baseline period was calculated for each patient by summing the daily MED for all opioid prescriptions dispensed to the patient during those 6 months. It reflects the maximum *prescribed* daily dose and not necessarily the actual amount *consumed*. Nonopioid medications also dispensed by VHA which can potentiate opioid-associated serious adverse effects, such as psychoactive drugs and nonopioid analgesics, were included as baseline variables [1,28]. Baseline health care utilization measures included the number of inpatient admissions and outpatient emergency department (ED), office, and pharmacy visits (Table 6).

Outcome Variable

The occurrence of serious opioid-related toxicity or overdose as defined by listed ICD-9-CM and CPT codes was the primary outcome variable (Table 1). All analyses were conducted at the patient level. For patients who experienced more than one episode of serious opioid-related respiratory/CNS depression or overdose during the study period, only the index event was evaluated.

Statistical Analysis

Baseline covariates and the outcome measure were summarized descriptively. Tests for normality were conducted, and medians and interquartile ranges (IQRs) were calculated for continuous variables that were not normally distributed. Frequencies and percentages were calculated for categorical variables. Student's *t*-tests or Wilcoxon Rank Sum tests were used, as appropriate, to examine differences in continuous variables of interest between cases and controls. Chi-squared tests of proportion were used to examine bivariate associations for categorical variables.

Multivariable analysis was performed using conditional logistic regression to examine factors potentially associated with the index event of serious opioid-related toxicity or overdose. The covariates included in the regression model were age, sex, race/ethnicity, marital status, US Census region, comorbidities, prescription opioid characteristics, the maximum prescribed daily MED, selected nonopioid prescription medications, and baseline health care resource utilization. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) and *P* values were calculated. *P* values less than 0.05 were considered statistically significant. One full, main effects, logistic regression model was run. Model discrimination was evaluated by the c-statistic which reflects the area under the receiver operating characteristic curve and ranges from 0.5 (no discrimination between cases and controls) to 1.0 (perfect discrimination) [41]. [43] Only the first (index) event of serious opioid-related toxicity or overdose was modeled for case patients who experienced more than one episode during the study period.

Table 2 Prescription opioids and morphine equivalent conversion factors

Opioid*	Morphine Equivalent Conversion Factor†,‡ (per mg of Opioid)
Short acting	
Meperidine hydrochloride	0.1
Codeine	0.15
Tramadol	0.2
Hydrocodone	1.0
Morphine sulfate	1.0
Oxycodone	1.5
Oxymorphone	3.0
Hydromorphone	4.0
Fentanyl citrate (transmucosal)	0.13§
Extended release/long-acting	
Morphine sulfate extended-release	1.0
Oxycodone hydrochloride controlled-release	1.5
Methadone	3.0
Fentanyl (transdermal)	2.4¶ **

* Some drug products contained an opioid in combination with a nonopioid (e.g., acetaminophen, aspirin) (Appendix II). No MED was calculated for the two controls who used sublingual buprenorphine.

† Sources of morphine equivalent conversion factors: Von Korff [37] and Leppert and Luczak [69].

‡ For each opioid dispensed, the daily MED (mg per day) was calculated as follows (see text): (number of units dispensed × strength of unit [mg] × MED conversion factor)/number of days supply.

§ Converting transmucosal fentanyl to morphine equivalents assumes 50% bioavailability of transmucosal fentanyl and that 100 µg of transmucosal fentanyl is equivalent to 12.5–15 mg of morphine.

¶ Converting transdermal fentanyl to morphine equivalents assumes that each patch has a conversion factor of 2.4 and remains in place for 3 days. The daily MED (mg per day) was calculated as follows:
(number of patches dispensed × 3 days per patch × strength of patch [µg/h] × MED conversion factor)/number of days supply.

** Prescription Drug Monitoring Program Training and Technical Assistance Center (no specific author) [41].

MED = morphine equivalent dose.

All analyses were conducted using SAS version 9.3 [44].

Results

Sixteen patients were excluded from the analysis due to missing age, sex, or race data. We identified 921 patients with a claim of life-threatening opioid-related respiratory/CNS depression or overdose and at least 6 months of continuous medical and pharmacy benefits before the event, 817 of whom were also dispensed an opioid by VHA. Among these 817 cases, 16 experienced more than one episode during the study period. Among those who received an opioid prescription from VHA during the study period, 8,170 control patients without overdose were identified who met selection criteria (Figure 1).

Descriptive Analysis

The median age was 62 years for both cases and controls (IQR, 10 and 16, respectively). As shown in Table 3, cases were more likely than controls to be non-Hispanic white, divorced, separated or widowed, and to reside in the western US Census region.

Compared with controls, patients with serious opioid-related toxicity or overdose were more likely to be diagnosed with other diseases and health conditions. The mean CCI score, which reflects general health status, was higher for cases than for controls (3.9 vs 1.7, $P < 0.0001$), indicating poorer overall health in the cases. As shown in Table 4, cases reported particularly significantly higher frequency during the 6-month baseline period of chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis); depression; skin ulcers; hypertension; malignancy; opioid dependence, substance abuse, nonopioid substance dependence, and tobacco use disorder; viral hepatitis; mental health disorders including anxiety, post traumatic stress, and bipolar disorders; cardiovascular disease; sleep apnea; back and neck disorders; neuropathic disorders; and traumatic injury (e.g., fracture, dislocation, contusion, laceration, wound).

VHA prescription drug dispensing data during the 6-month baseline period indicated that, overall, cases were prescribed opioids significantly more often than controls, in larger variety, with a higher proportion of extended-release or long-acting (ER/LA) formulations and with a higher mean maximum prescribed daily MED (Table 5). The mean number of opioid prescriptions dispensed in the baseline period was 6.8 among cases, compared with 2.5 among controls ($P < 0.0001$). Prescription opioid active ingredients varied significantly between cases and controls, with more hydrocodone, methadone, oxycodone, and morphine, but less tramadol, dispensed to cases than controls. Both ER/LA and short-acting formulations as well as oral opioids were prescribed to cases more often than to controls. The mean maximum prescribed MED was 122 mg per day in cases and 48 mg per day in controls, with significantly more cases receiving prescriptions for MED ≥50 mg per day and ≥100 mg per day. All selected nonopioid drugs were also prescribed to cases significantly more often than to controls (Table 5).

As shown in Table 6, cases had significantly greater health care resource utilization than controls during the baseline period, including outpatient office and ED visits, hospital-

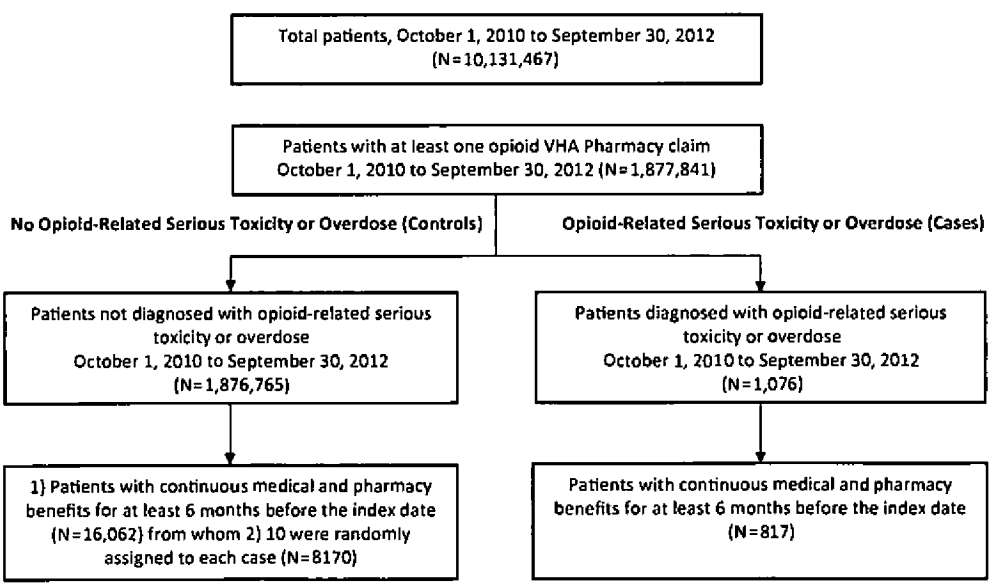


Figure 1 Sample selection flowchart.

Table 3 Baseline demographic characteristics

	Cases (N = 817)		Controls (N = 8,170)		
Characteristics	N	SD, %	N	SD, %	*P*
Age (years), median (IQR)	62.0	10.0	62.0	16.0	<0.001
Age group (years)					
18–34	27	3.3	565	6.9	<0.001
35–44	31	3.8	619	7.6	<0.001
45–54	115	14.1	1,240	15.2	0.402
55–64	377	46.1	2,672	32.7	<0.001
65+	267	32.7	3,074	37.6	0.005
Male	753	92.2	7,528	92.1	0.980
Race/ethnicity					
Non-Hispanic white	555	67.9	4,546	55.6	<0.001
Non-Hispanic black	83	10.2	1,300	15.9	<0.001
Hispanic	32	3.9	431	5.3	0.094
Other	147	18.0	1,893	23.2	0.001
Marital status					
Never married	102	12.5	1,227	15.0	0.052
Married	351	43.0	4,246	52.0	<0.001
Separated	20	2.5	41	0.5	<0.001
Divorced	285	34.9	2,268	27.8	<0.001
Widowed	59	7.2	388	4.8	0.002
BMI (kg/m^2)					
Underweight (<18.5)	29	3.6	72.0	0.9	<0.001
Normal (18.5–24.9)	193	23.6	1,197	14.7	<0.001
Overweight (25.0–29.9)	224	27.4	2,070	25.3	0.193
Obese (≥30.0)	306	37.5	2,667	32.6	0.005
Missing	65	8.0	2,164	26.5	<0.001
US Census region					
Northeast	75	9.2	824	10.1	0.411
North Central	190	23.3	1,745	21.4	0.208
South	270	33.1	3,258	39.9	<0.001
West	257	31.5	1,842	22.6	<0.001
Other	25	3.1	501	6.1	<0.001

BMI = body mass index; IQR = interquartile range; SD = standard deviation.

izations, and pharmacy visits. An ED visit occurred during the baseline period in 65% of cases compared with 21% of controls. Nearly half of the cases were hospitalized during the baseline period at least once compared with 9% of controls.

During the 2-year study period, 159/817 case patients died (19.5%) compared with 282/8,170 controls (3.5%). Twenty of the deaths in the case patients occurred during a VHA-treated episode of serious toxicity or overdose for an index event fatality rate of 2.4% (20/817).

Multivariable Analysis

The logistic regression model for the dichotomous outcome of serious opioid-related respiratory/CNS depression or overdose resulted in multiple, independent, statistically significant associations. To improve the estimate stability, the marital status categories "separated" (N = 20/817 cases) and "divorced" (N = 285/817 cases) were combined into one category. Endocarditis was not included in the final logistic regression as it was reported in only one case patient. The final model yielded a c-statistic of 0.89. As displayed in Figure 2, significant independent demographic predictors of serious opioid toxicity included ages 55–64 years and 65 and above, non-Hispanic white race, never married, widowed, and those receiving care in the western region of the United States.

Concomitant health conditions that were most strongly associated with the occurrence of serious opioid-related toxicity or overdose were opioid dependence, moderate or severe liver disease, skin ulcers, metastatic solid tumor, and pancreatitis. Other comorbidities significantly associated with the outcome included renal disease, bipolar disorder, traumatic injury chronic pulmonary disease, warfarin use, substance abuse, and sleep apnea (Figure 3).

Prescription opioids containing hydromorphone or oxycodone and those with ER/LA formulations were

Table 4 Baseline clinical characteristics

	Cases (N = 817)		Controls (N = 8,170)		
Comorbidities	N	SD, %	N	SD, %	*P*
CCI score, mean (SD)	3.9	3.3	1.7	2.0	<0.001
Individual CCI comorbidities					
Myocardial infarction	28	3.4	105	1.3	<0.001
Congestive heart failure	93	11.4	308	3.8	<0.001
Peripheral vascular disease	71	8.7	353	4.3	<0.001
Cerebrovascular disease	57	7.0	343	4.2	<0.001
Dementia	5	0.6	32	0.4	0.348
Chronic pulmonary disease	291	35.6	1,047	12.8	<0.001
Rheumatologic disease	6	0.7	96	1.2	0.257
Peptic ulcer disease	9	1.1	63	0.8	0.312
Mild liver disease	43	5.3	64	0.8	<0.001
Diabetes	263	32.2	1,850	22.6	<0.001
Hypertension	495	60.6	3,670	44.9	<0.001
Depression	357	43.7	1,562	19.1	<0.001
Use of warfarin	78	9.6	387	4.7	<0.001
Hemiplegia or paraplegia	13	1.6	34	0.4	<0.001
Renal disease	112	13.7	428	5.2	<0.001
Any malignancy, including leukemia and lymphoma	147	18.0	646	8.0	<0.001
Diabetes with chronic complications	92	11.3	432	5.3	<0.001
Skin ulcers	122	14.9	302	3.7	<0.001
Moderate or severe liver disease	28	3.4	19	0.2	<0.001
Metastatic solid tumor	46	5.6	59	0.7	<0.001
HIV/AIDS	11	1.4	42	0.5	0.003
Other selected comorbidities					
Nonpain related					
Substance abuse and nonopioid substance dependence	215	26.3	764	9.4	<0.001
Opioid dependence	105	12.9	97	1.2	<0.001
Endocarditis	1	0.1	9	0.1	0.920
Viral hepatitis	106	13.0	249	3.0	<0.001
Alcoholic hepatitis	3	0.4	5	0.1	0.005
Pancreatitis	24	2.9	49	0.6	<0.001
Sexually transmitted disease	12	1.5	69	0.8	0.072
Herpes simplex infection	7	0.9	45	0.6	0.272
Skin infections/abscesses	85	10.4	286	3.5	<0.001
Sleep apnea	147	18.0	652	8.0	<0.001
Tobacco use disorder	301	36.8	1,266	15.5	<0.001
PTSD	221	27.1	1,119	13.7	<0.001
Bipolar disorder	86	10.5	239	2.9	<0.001
ADHD	7	0.9	58	0.7	0.637
Schizophrenia	36	4.4	114	1.4	<0.001
Anxiety disorder	180	22.0	681	8.3	<0.001
OCD	5	0.6	19	0.2	0.045
Cardiovascular disease	172	21.1	764	9.4	<0.001
Obesity	150	18.4	1,072	13.1	<0.001
Pain related					
Low back disorders	380	46.5	2,099	25.7	<0.001
Other back/neck disorders	214	26.2	1,048	12.8	<0.001
Neuropathic disorders	170	20.8	717	8.8	<0.001
Fibromyalgia	34	4.2	157	1.9	<0.001
Headache/migraine	88	10.8	427	5.2	<0.001
Burns	4	0.5	16	0.2	0.089
Traumatic injury	212	26.0	869	10.6	<0.001
Motor vehicle accidents	7	0.9	14	0.2	<0.001

ADHD = attention deficit hyperactivity disorder; AIDS = acquired immunodeficiency syndrome; CCI = Charlson Comorbidity Index, 2008 updated (score); OCD = obsessive–compulsive disorder; PTSD = post-traumatic stress disorder; SD = standard deviation.

Table 5 Baseline prescription drugs dispensed by VHA

	Cases (N = 817)		Controls (N = 8,170)		
Prescription Drug Use	N	SD, %	N	SD, %	*P*
Opioid use	693	84.8	4,936	60.4	<0.001
By active ingredient					
Hydrocodone	314	38.4	2,633	32.2	<0.001
Oxycodone	305	37.3	876	10.7	<0.001
Buprenorphine	0	0.0	2	0.0	0.655
Tramadol	114	14	1,428	17.5	0.011
Codeine	63	7.7	561	6.9	0.365
Fentanyl	49	6.0	44	0.5	<0.001
Morphine	251	30.7	334	4.1	<0.001
Hydromorphone	38	4.7	28	0.3	<0.001
Methadone	107	13.1	139	1.7	<0.001
Oxymorphone	1	0.1	1	0.0	0.044
Other*	2	0.2	4	0.1	0.039
By formulation					
ER/LA‡	369	45.2	499	6.1	<0.001
Short acting‡	633	77.5	4,807	58.9	<0.001
Proportion of opioids = ER/LA†	0.25	0.3	<0.1	0.2	<0.001
By route					
Oral	692	84.7	4,923	60.3	<0.001
Parenteral	6	0.7	6	0.1	<0.001
Transdermal	48	5.9	44	0.5	<0.001
Number of opioid prescriptions dispensed, mean (SD)	6.8	5.9	2.5	3.4	<0.001
Number of unique opioid NDCs, mean (SD)	2.4	1.9	0.9	1.1	<0.001
Maximum prescribed daily MED (mg), mean (SD)	98.7	122.1	24.2	48.4	<0.001
1–<20	35	4.3	1,331	16.3	<0.001
20–<50	227	27.8	2,614	32.0	0.014
50–<100	163	20.0	718	8.8	<0.001
≥100	268	32.8	273	3.3	<0.001
Selected nonopioid drugs	747	91.4	5,905	72.3	<0.001
Benzodiazepines	336	41.1	1,242	15.2	<0.001
Antidepressants	565	69.2	2,886	35.3	<0.001
Nonopioid analgesics	556	68.1	4,598	56.3	<0.001
Muscle relaxants	226	27.7	1,288	15.8	<0.001
Other sedatives	125	15.3	609	7.5	<0.001
Antipsychotics	239	29.3	772	9.5	<0.001
Stimulants	14	1.7	51	0.6	<0.001

* Other opioids include meperidine and pentazocine/naloxone.
† Proportion of opioid prescriptions dispensed to a patient during baseline that contained an ER/LA formulation. Methadone is a long-acting opioid.
‡ Percentages exceed 100% due to prescription of both ER/LA and short-acting formulations in some patients.
ER/LA = extended release/long acting; MED = morphine equivalent dose; NDC = National drug code; SD = standard deviation; VHA = Veterans Health Administration.

significantly associated with increased risk of serious opioid-related toxicity or overdose. The likelihood of experiencing the outcome was related monotonically to increasing maximum prescribed daily MED of 20 mg or higher. Patients prescribed a maximum daily MED ≥100 mg during the baseline period were more than four times as likely to experience serious opioid-related toxicity or overdose compared with those prescribed MED of 1–<20 mg/day, whereas patients prescribed 50–<100 mg/day MED were 2.2 times as likely, and those prescribed 20–49 mg/day MED were 1.5 times as likely to experience life-threatening opioid-related respiratory/CNS depression or overdose (Figure 4). Coprescription of benzodiazepines, antidepressants, and antipsychotics in opioid users was significantly associated with experiencing serious toxicity or overdose.

Patients hospitalized for one or more days for any reason during the baseline period were nearly three times as likely to experience serious opioid-related toxicity compared with those who were not hospitalized.

Table 6 Baseline health care utilization

All-Cause Health Care Utilization	Cases (N = 817)		Controls (N = 8,170)		
	N	SD, %	N	SD, %	*P*
Days of hospitalization, mean (SD)	9.6	22.9	1.1	8.0	<0.001
Patients with ≥1 outpatient ED visit	534	65.4	1,740	21.3	<0.001
Patients with ≥1 outpatient office visit	792	96.9	7,333	89.8	<0.001
Patients with ≥1 inpatient hospitalization	396	48.5	739	9.1	<0.001
Patients with ≥1 prescription fill	800	97.9	7,561	92.6	<0.001
Outpatient ED visits per patient, mean (SD)	2	2.6	0.4	1	<0.001
Outpatient office visits per patient, mean (SD)	23	18.6	9.8	11.3	<0.001
Inpatient hospitalizations per patient, mean (SD)	1	1.5	0.1	0.5	<0.001
Pharmacy visits per patient, mean (SD)	24.6	15.0	12.9	10.4	<0.001

ED = emergency department; SD = standard deviation.

Full regression results, including factors that were not statistically significantly related to the outcome in the logistic model are provided in Appendix II.

Discussion

Our study produced a robust multivariable model that characterized the risk of life-threatening opioid-related respiratory/CNS depression or overdose in medical users of prescription opioids. Higher maximum prescribed daily MED, a history of opioid dependence, and hospitalization during the 6 months before the overdose or serious toxicity event were the factors most strongly associated with this outcome among an opioid-exposed cohort of predominantly US veterans. Consistent with published findings on prescription opioid overdose *deaths*, we found that certain demographic characteristics, comorbid conditions, and medication-related factors were associated with non-fatal prescription opioid-related serious toxicity or overdose as well [16,21,45]. Demographic variables previously identified as risk factors, and confirmed in the present study, included non-Hispanic white race, never married and widowed marital status, and residence in the Western United States [2,12,16,21,24,45,46]. These factors are likely to be proxies for underlying patient-related constructs, including genetic influences on drug metabolism; the social environment, such as isolation; the prescriber, including opioid-prescribing patterns; and the

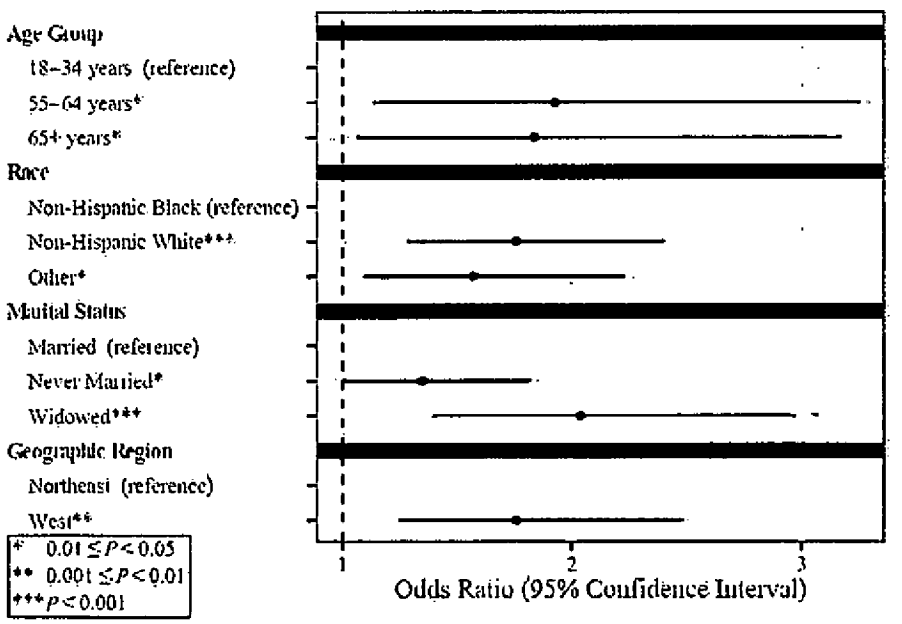


Figure 2 Logistic regression results: significant demographic factors.

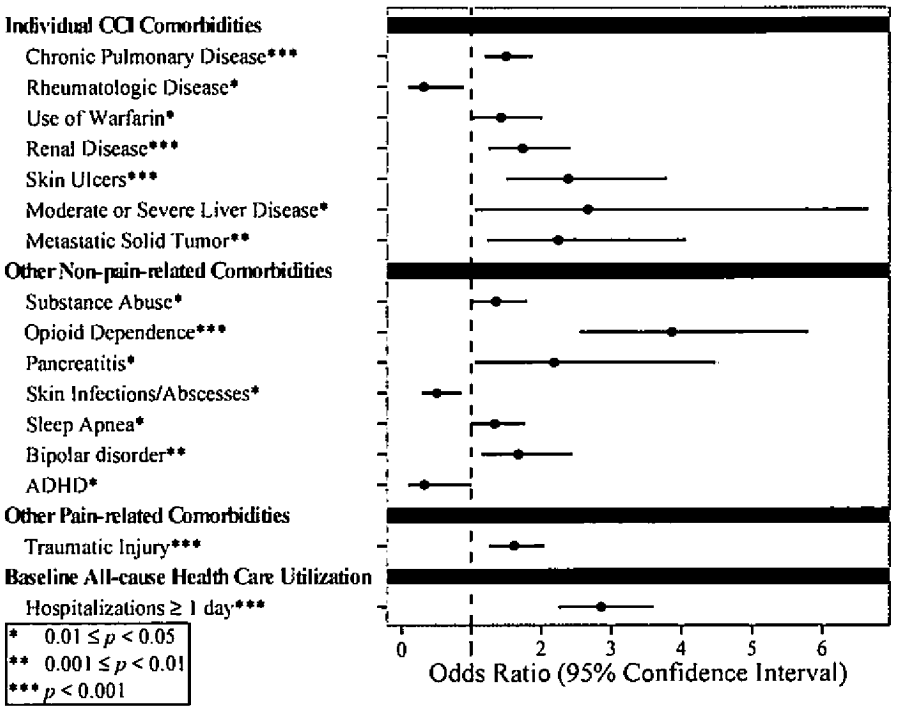


Figure 3 Logistic regression results: significant comorbid conditions and health care utilization factors.

health care system, such as access to emergency care and other medical services [24,47–52].

Some of our findings differed from those of studies of fatal opioid overdose. In contrast to the typical occurrence of opioid overdose death in middle age (peaking at 45–54 years), most case patients in our study were aged 55 years or older [8,12]. This discrepancy likely reflects the older VHA population. The older age predominance also affected the pattern of comorbidity in our study population, with chronic diseases and cancer being prevalent. Physiologically older individuals have age-related impairment in the hepatic and renal ability to metabolize and excrete certain drugs and other substances and have a greater burden of disease and associated potentially interacting concomitant medications. Such individuals are biologically vulnerable to opioid accumulation and to experiencing toxicity even when using an opioid well within its recommended dosing range. The safe use of opioids long-term to manage chronic pain in elderly patients is particularly challenging [39,53–55].

Another reported treatment challenge observed in our study population was the strong association of serious respiratory/CNS depression or overdose with substance use disorders (dependence and abuse) and mental health disorders (bipolar disorder). Abuse of alcohol, illicit opioids, and other substances is more frequent among medical users of prescription opioids than in the general population or chronic pain patients not treated with opioids [11,33,56]. We observed that polypharmacy with psychoactive drugs commonly prescribed for mental health disorders, such as benzodiazepines, antidepressants, and antipsychotics, as well as mental illness itself, was involved in approximately one-half of overdose events [1,13,56,57]. The association between serious toxicity events among opioid users in this study and pharmacotherapy for mental health disorders such as depression and anxiety may be partially mediated by the substantially higher prevalence of substance use disorders [56].

We found certain opioid characteristics to be highly associated with the likelihood of experiencing opioid-related toxicity or overdose. Use of extended-release formulations and long-acting opioids was strongly associated with an increased likelihood of overdose events, as reported previously [27,30,58]. Methadone, a long-acting opioid, was also examined as an independent determinant due to its long half-life, variable pharmacokinetics, and disproportionate involvement in 30–40% of all opioid-related deaths despite accounting for only 5–19% of US opioids prescribed [7,12,18,27,59]. In contrast to other studies that focused exclusively on *fatal* overdose, methadone alone was not independently associated with serious respiratory/CNS depression or overdose events treated at VHA facilities, falling just short of the statistical significance threshold ($P = 0.08$). It is unclear whether this difference is due to the study sample's relatively low prevalence of

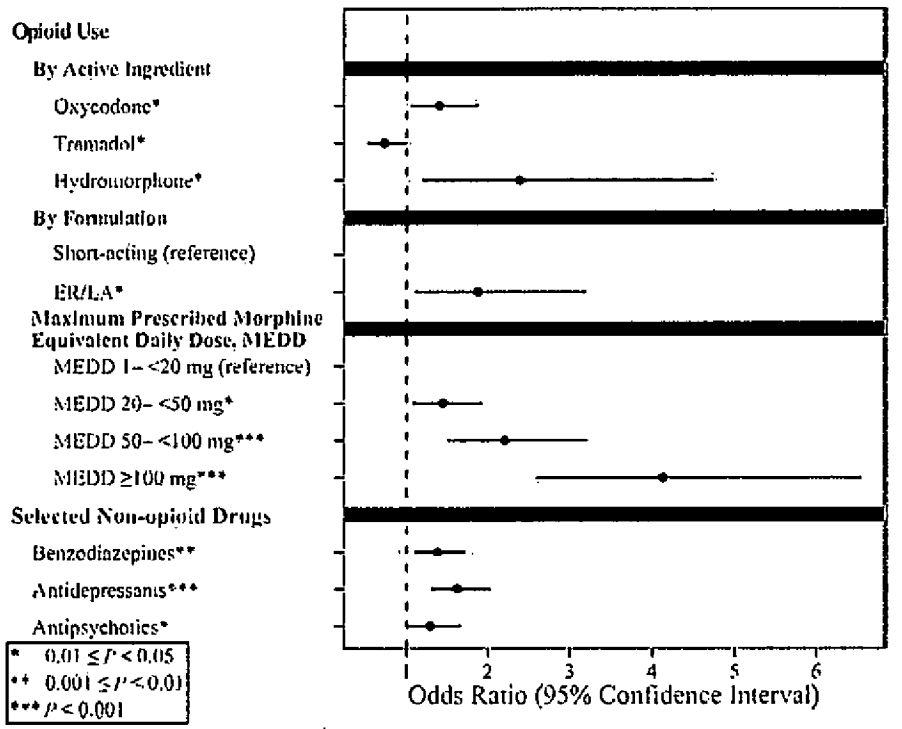


Figure 4 Logistic regression results: significant prescription drug-related factors.

methadone dispensed and fatal outcomes or to other characteristic(s) of the study sample or model specification.

Our study confirmed the known dose-related toxicity of opioids. Importantly, maximum prescribed daily MED of as little as 20 mg was associated with serious fatal and nonfatal overdose and toxicity in opioid consumers overall. Previous research identified a significant risk of overdose death for daily MED of ≥20 or 50 mg in patients with chronic noncancer pain [21,25,60]. An increasing body of scientific evidence suggests that prescriber overreliance on, and inadequate proficiency using, opioid dose conversion factors or ratios in published equianalgesic dose tables to calculate MED is an important contributor in fatal or near-fatal opioid-related CNS/respiratory depression [27,38,61–64]. The numerous published equianalgesic tables that are widely available contain inconsistent and variable conversion ratios. To reduce the risk of unintentional serious toxicity when rotating or switching opioids, updated guidelines for the safe use of equianalgesic dose tables emphasize the need to consider the opioid conversion ratio or calculated equianalgesic dose in morphine equivalents as only an approximate starting point. The calculated MED must then be adjusted for each individual patient and clinical scenario by accounting for interindividual sources of variation that can alter opioid potency. Such sources of individual variation include demographic differences (age, sex, race, ethnicity), major organ impairment (liver, kidney, adrenal), potential interactions with concomitant nonopioid medications and substances (e.g., benzodiazepines, alcohol), the direction of the opioid switch, and incomplete cross tolerance between opioids, as well as differences in the likelihood of opioid-induced hyperalgesia and physical dependence. Some differences may be due to significant genetic variants in opioid receptors, metabolism, and transport in the nervous system [65,66]. The current guidelines are based on expert opinion and have not been validated for safety or efficacy [55,61,64,67].

Of note, medical use of tramadol in our study appeared to be protective against serious opioid-related overdose (OR 0.7, 95% CI, 0.5–1.0). Tramadol, a novel synthetic opioid analgesic with monamine reuptake inhibition contributing to its analgesic effect, has low mu opioid receptor binding affinity and is not currently regulated as a controlled substance at the federal level in the United States [68–71]. However, its US prescribing information contains warnings similar to all prescription opioids regarding the risk of CNS and respiratory depression, overdose, and death. This interesting study finding warrants further investigation.

Pain is a complex, multidimensional condition with a multiplicity of interacting and contributing influences [72]. Factors involved in the likelihood of serious opioid-related toxicity or overdose in individuals treated for painful conditions relate to the patient and their social environment,

prescriber or other source of opioids, health care system, and the specific opioid and other exposures. Although pain is the most common reason a patient seeks medical care, current US data on the incidence, prevalence, and treatment of pain are not complete or consistent, partly because it is considered a symptom. Recent evidence indicates that approximately 80% of episodes of pain treated with opioids are short term [37]. However, an estimated 100–116 million US adults suffer chronic pain [53,72], and 3–4% of the adult population (9 million) are prescribed opioids each year to manage chronic noncancer pain [6–9,11]. Thus, the total population at risk of life-threatening opioid-related respiratory/CNS depression or overdose is substantial.

Our study confirms and extends findings from prior research that focused on fatal overdoses but did not differentiate between medical and nonmedical opioid users [13,16–18,21,60]. The relatively low frequency of fatal outcomes of serious opioid-related events in our VHA-treated cohort (2.4% over 2 years) suggests that the majority of such events in medical users is not fatal. However, nonfatal events do place a substantial burden on the health care system and patients [73,74].

Strengths and Limitations

Major strengths of this study include the large, national patient population as well as the rich detail of VHA administrative data. The robust statistical model included variables that are readily available from medical and pharmacy claims data. In contrast to most previous research, we examined in a comprehensive and systematic fashion the determinants associated with nonfatal as well as fatal serious toxicity and overdose related to the medical use of prescription opioids. However, the study sample included all opioid-exposed patients and was stratified by neither therapeutic indication or acuity (e.g., acute vs chronic pain conditions; chronic pain related to cancer vs noncancer) nor by the duration of opioid treatment (short term vs long term), partly to avoid potential statistical challenges with the limited number of cases available. Our study was subject to many of the limitations commonly associated with observational studies using administrative data (e.g., limited ability to infer causality and limited access to information regarding actual medication consumption/adherence, other behavioral/social elements, and therapeutic indication, with the potential for residual confounding). In addition, while VHA provides a large, national population from which to sample, generalizability is limited as the population comprises primarily older, white men who receive most of their health care within a single, closed system.

Limitations in accuracy and completeness are inherent in administrative data and include missing data, coding errors, misclassification, and undiagnosed or undocumented comorbidities such as substance use disorders. While prescriptions dispensed within the VHA system are well documented, it is possible that patients in the study also consumed opioids and other medications or substances from unreported non-VHA sources, particularly in the case cohort which had a significantly higher prevalence of substance use disorders. In addition, the serious respiratory/CNS depression and overdose rate in this sample is likely an underestimate as we evaluated only cases that fulfilled a stringent case definition and came to medical attention within VHA.

Implications for Future Research

Future studies should assess the generalizability of these findings to populations more representative of US medical users of prescription opioids, including wider age ranges and more women. With a larger dataset, selected interactions among risk factors should be evaluated, as well as the predictive utility of behavioral and other factors not routinely captured in administrative health care data (e.g., use of alcohol and other substances, other sources of opioids, therapeutic indication, social conditions, setting of the overdose or serious toxicity event, family history). Potential differences in risk factor profiles for overdose or life-threatening respiratory/CNS depression among those treated with opioids for acute vs chronic conditions, chronic noncancer pain vs chronic cancer pain, and short term vs long term should also be explored.

Conclusions

The risk of life-threatening toxicity, including overdose, in medical users of prescription opioids is an alarming, escalating public health problem. Substantial risk exists when even relatively low daily MED of opioids is used in patients who are vulnerable due to sociodemographic factors, concomitant medical and psychiatric conditions, and simultaneous use of other medications or substances. Expert guidelines recommend screening all patients before initiating opioids for pain management to identify those at elevated risk for serious adverse outcomes [26,55,75]. An extensive literature review revealed several available instruments to screen for aberrant drug-related behaviors (abuse, addiction, diversion) [55,76], but no instruments that provide useful, real-time, evidence-based information to the prescriber regarding the risk of overdose or serious respiratory/CNS depression currently exist [55]. A public health imperative is the identification of medical users of prescription opioids who are at highest risk of life-threatening toxicity for whom additional precautions should be considered. These precautions include education of the patient and caregivers, increased caution in opioid selection and dose escalation, consultation with pain management specialists, and close monitoring for the emergence of opioid-related toxicity or known risk factors for this outcome [28,55,75]. Additional measures to reduce opioid-related morbidity and mortality may include enhanced training and compliance of health care providers with evidence-based best practices for prescribing opioids, such as considering coprescribing naloxone, particularly if delivery systems can be developed that are safe and more user friendly for nonmedical first responders than the current syringe or nasal atomizer-based systems. Naloxone is a rescue medication with more than three

decades of proven effectiveness and safety in reversing life-threatening opioid-related respiratory/CNS depression or overdose [3,7,74,77–80].

The results of our study indicate that a statistically robust model based on administrative medical, pharmacy, and health care resource utilization data may help identify the demographic characteristics, comorbid conditions, concomitant medications, and opioid-related factors associated with increased risk of life-threatening toxicity and overdose. These factors help to identify the individuals most likely to benefit from preventive interventions. The development and widespread use of a risk profiling questionnaire based on these factors to guide patient treatment decisions would have the potential to significantly improve the balance between the analgesic benefit of opioid therapy and the risks of serious toxicity or overdose and other adverse outcomes, including abuse, diversion for nonmedical use, and iatrogenic addiction.

Acknowledgments

The authors of the study would like to acknowledge Juan Du, MS, of STATinMED, Inc. for statistical programming support and Elizabeth Moran of STATinMED, Inc. for medical writing support on this project.

References

1 Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013; 309(7):657–9.

2 Centers for Disease Control and Prevention. Vital signs: Overdoses of prescription opioid pain relievers—United States, 1999–2008. MMWR Morb Mortal Wkly Rep 2011;60(43):1487–92.

3 SAMHSA Opioid Overdose Prevention Toolkit: Information for Prescribers. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013. HHS Publication No. (SMA) 13-4742.

4 Jungquist CR, Karan S, Perlis ML. Risk factors for opioid-induced excessive respiratory depression. Pain Manag Nurs 2011;12(3):180–7.

5 Stephens E, Louden M, VanDe Voort J, et al. Opioid Toxicity: Medscape. 2012. Available at: http://emedicine.medscape.com/article/815784-overview (accessed December 2013); updated October 23, 2012, accessed December 8 2013.

6 Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf 2009;18(12):1166–75.

7 CDC Grand Rounds. Prescription Drug Overdoses—A US Epidemic. MMWR Morb Mortal Wkly Rep 2012;61(1):10–3.

8 Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: A ten-year perspective. Pain Physician 2010;13(5):401–35.

9 Parsells Kelly J, Cook SF, Kaufman DW, et al. Prevalence and characteristics of opioid use in the US adult population. Pain 2008;138(3):507–13.

10 Sullivan MD, Edlund MJ, Fan MY, et al. Trends in use of opioids for non-cancer pain conditions 2000–2005 in commercial and Medicaid insurance plans: The TROUP study. Pain 2008;138(2):440–9.

11 Sullivan MD, Edlund MJ, Steffick D, Unutzer J. Regular use of prescribed opioids: Association with common psychiatric disorders. Pain 2005;119(1–3):95–103.

12 Warner M, Chen LH, Makuc DM, Anderson RN, Minino AM. Drug poisoning deaths in the United States, 1980–2008. NCHS Data Brief 2011;(81): 1–8.

13 Paulozzi LJ, Kilbourne EM, Shah NG, et al. A history of being prescribed controlled substances and risk of drug overdose death. Pain Med 2012;13(1):87–95.

14 American Academy of Pain Medicine and the American Pain Society. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain 1997;13:6–8.

15 Centers for Disease Control and Prevention. Vital Signs. Overdoses of prescription opioid pain relievers and other drugs among women—United States, 1999–2010. Morb Mortal Wkly Rep 2013; 62(26):537–42.

16 Lanier WA, Johnson EM, Rolfs RT, Friedrichs MD, Grey TC. Risk factors for prescription opioid-related death, Utah, 2008–2009. Pain Med 2012;13(12): 1580–9.

17 Madadi P, Hildebrandt D, Lauwers AE, Koren G. Characteristics of opioid-users whose death was related to opioid-toxicity: a population-based study in Ontario, Canada. PLoS One. 2013;8(4): e60600.

18 Paulozzi LJ, Logan JE, Hall AJ, et al. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. Addiction 2009; 104(9):1541–8.

19 Wunsch MJ, Nakamoto K, Behonick G, Massello W. Opioid deaths in rural Virginia: A description of the high prevalence of accidental fatalities involving prescribed medications. Am J Addict 2009;18(1):5–14.

20 Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA 2008;300(22):2613–20.

21 Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011;305(13):1315–21.

22 Substance Abuse and Mental Health Services Administration. Results from the 2009 National Survey on Drug Use and Health: volume 1: summary of national findings. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2010.

23 Coolen P, Best S. Overdose Deaths Involving Prescription Opioids Among Medicaid Enrollees—Washington, 2004–2007. Atlanta, Ga: Centers for Disease Control and Prevention, 2009 Contract No.: 42.

24 McDonald DC, Carlson K, Izrael D. Geographic variation in opioid prescribing in the U.S. J Pain 2012; 13(10):988–96.

25 Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: A cohort study. Ann Intern Med 2010;152(2):85–92.

26 Joint Commission on Accreditation of Health Care Organizations. Safe use of opioids in hospitals: Joint Commission on Accreditation of Health Care Organizations. 2012. Available at: http://www.jointcommission.org/assets/1/18/SEA_49_opioids_8_2_12_final.pdf (accessed December 2013).

27 Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. Pain Med 2011;12(suppl 2):S26–35.

28 Nuckols TK, Anderson L, Popescu I, et al. Opioid prescribing: A systematic review and critical appraisal of guidelines for chronic pain. Ann Intern Med 2013; 160(1):38–47.

29 Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med 2010;170(16):1425–32.

30 Morasco BJ, Duckart JP, Carr TP, Deyo RA, Dobscha SK. Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain. Pain 2010;151(3):625–32.

31 Centers for Disease Control and Prevention. ICD-9-CM Official Guidelines for Coding and Reporting: Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nchs/data/icd9/icd9cm_guidelines_2011.pdf (accessed November 2013).

32 Charlson ME, Charlson RE, Peterson JC, et al. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. J Clin Epidemiol 2008;61(12):1234–40.

33 Baser O, Xie L, Mardekian J, et al. Prevalence of Diagnosed Opioid Abuse and its Economic Burden in the Veterans Health Administration. Pain Pract 2013.

34 Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain 2007; 8(7):573–82.

35 Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med 2007;3(5):455–61.

36 Xie L, Joshi AV, Schaaf D, et al. Differences in Healthcare Utilization and Associated Costs Between Patients Prescribed vs. Nonprescribed Opioids During an Inpatient or Emergency Department Visit. Pain Pract 2013.

37 Von Korff M, Saunders K, Ray GT, Boudreau D, Campbell D, Merrill J, et al. Defacto long-term opioid therapy for non-cancer pain. Clin J Pain 2008; 24(6):521–7.

38 Vieweg WV, Lipps WF, Fernandez A. Opioids and methadone equivalents for clinicians. Prim Care Companion J Clin Psychiatry 2005;7(3):86–8.

39 Miaskowski C, Bair M, Chou R, D'Arcy Y, Hartwick C, Huffman L, et al., Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. Sixth ed. Glenview, IL: American Pain Society; 2008. p. 19–38.

40 Fine PG, Portenoy RK. A Clinical Guide to Opioid Analgesia. Minneapolis: McGraw Hill; 2004.

41 Technical Assistance Guide No. 01-13: Calculating Daily Morphine Milligram Equivalents: Prescription Drug Monitoring Program Training and Technical Assistance Center. 2013. Available at: http://www.pdmpassist.org/pdf/BJA_performance_measure_aid_MME_conversion.pdf (accessed March 2014). updated Feb 28 2013.

42 Prescription Drug Monitoring Program Training and Technical Assistance Center. Technical Assistance Guide No. 02-13: Daily Morphine Milligram Equivalents Calculator and Guide.: Prescription Drug Monitoring Program Training and Technical Assistance Center. 2013. Available at: http://www.pdmpassist.org/pdf/bja_performance_measure_aid_mme_conversion_tool.pdf (accessed March 2014). updated May 1 2013.

43 Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation 2007;115(7):928–35.

44 SAS. 9.3. SAS Institute. Cary, NC. 2013.

45 Cerda M, Ransome Y, Keyes KM, et al. Prescription opioid mortality trends in New York City, 1990–2006: Examining the emergence of an epidemic. Drug Alcohol Depend 2013;132(1–2):53–62.

46 Johnson EM, Lanier WA, Merrill RM, et al. Unintentional prescription opioid-related overdose deaths: Description of decedents by next of kin or best contact, Utah, 2008–2009. J Gen Intern Med 2013;28(4):522–9.

47 Johnson JA. Ethnic differences in cardiovascular drug response: Potential contribution of pharmacogenetics. Circulation 2008;118(13):1383–93.

48 Joung IM, van de Mheen H, Stronks K, van Poppel FW, Mackenbach JP. Differences in self-reported morbidity by marital status and by living arrangement. Int J Epidemiol 1994;23(1):91–7.

49 Joung IM, van der Meer JB, Mackenbach JP. Marital status and health care utilization. Int J Epidemiol 1995;24(3):569–75.

50 Mor A, Ulrichsen SP, Svensson E, Berencsi K, Thomsen RW. Does marriage protect against hospitalization with pneumonia? A population-based case-control study. Clin Epidemiol 2013;5:397–405.

51 Aizer AA, Chen MH, McCarthy EP, et al. Marital status and survival in patients with cancer. J Clin Oncol 2013;31(31):3869–76.

52 Sammon JD, Morgan M, Djahangirian O, et al. Marital status: A gender-independent risk factor for poorer survival after radical cystectomy. BJU Int 2012;110(9):1301–9.

53 National Institute on Drug Abuse. Prescription Drugs: Abuse and Addiction. Older Adults. Available at: www.drugabuse.gov/publications/research-reports/prescription-drugs/trends-in-prescription-drug-abuse/older-adults (accessed October 2013).

54 American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older P. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009;57(8):1331–46.

55 Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009;10(2):113–30.

56 Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? Pain Med 2007;8(8):647–56.

57 Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA 2012;307(9):940–7.

58 Food and Drug Administration. FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. US Food and Drug Administration. 2013.

59 Centers for Disease Control and Prevention. Vital Signs: Risk for overdose from methadone used for pain relief—United States, 1999–2010. MMWR Morb Mortal Wkly Rep 2012;61(26):493–7.

60 Gomes T, Juurlink DN, Dhalla IA, et al. Trends in opioid use and dosing among socio-economically disadvantaged patients. Open Med 2011;5(1):e13–22.

61 Fine PG, Portenoy RK, Ad Hoc Expert Panel on Evidence R, Guidelines for Opioid R. Establishing "best practices" for opioid rotation: Conclusions of an expert panel. J Pain Symptom Manage 2009;38(3):418–25.

62 McNicol E. Opioid equianalgesic conversions. J Pain Palliat Care Pharmacother 2009;23(4):459.

63 Shaheen PE, Walsh D, Lasheen W, Davis MP, Lagman RL. Opioid equianalgesic tables: Are they all equally dangerous? J Pain Symptom Manage 2009;38(3):409–17.

64 Webster LR, Fine PG. Review and critique of opioid rotation practices and associated risks of toxicity. Pain Med 2012;13(4):562–70.

65 Kalvass JC, Olson ER, Cassidy MP, Selley DE, Pollack GM. Pharmacokinetics and pharmacodynamics of seven opioids in P-glycoprotein-competent mice: Assessment of unbound brain EC50,u and correlation of in vitro, preclinical, and clinical data. J Pharmacol Exp Ther 2007;323(1):346–55.

66 Liang DY, Liao G, Lighthall GK, Peltz G, Clark DJ. Genetic variants of the P-glycoprotein gene Abcb1b modulate opioid-induced hyperalgesia, tolerance and dependence. Pharmacogenet Genomics 2006;16(11):825–35.

67 Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. J Pain Symptom Manage 2001;22(2):672–87.

68 US Veterans' Health Affairs Administration. Veterans Administration/Department of Defense Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain. 2010. Available at: http://www.va.gov/painmanagement/docs/cpg_opioidtherapy_fulltext.pdf (accessed March 2014).

69 Leppert W, Luczak J. The role of tramadol in cancer pain treatment—A review. Support Care Cancer 2005;13(1):5–17.

70 Drug Enforcement Administration. Tramadol, Drug and Chemical Evaluation. US Drug Enforcement Administration, Office of Diversion Control. August 29 2013. Available at: http://www.deadiversion.usdoj.gov/drug_chem_info/tramadol.pdf (accessed March 2014).

71 Tramadol Label. Daily Med: Current Medication Information. National Library of Medicine. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=45f59e6f-1794-40a4-8f8b-3a9415924468 (accessed March 2014).

72 Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press; 2011.

73 Inocencio TJ, Carroll NV, Read EJ, Holdford DA. The economic burden of opioid-related poisoning in the United States. Pain Med 2013;14(10):1534–1547.

74 Albert S, Brason FW, Sanford CK, et al. Project Lazarus: Community-based overdose prevention in rural North Carolina. Pain Med 2011;12(suppl 2):S77–85.

75 Furlan AD, Reardon R, Weppler C. Opioids for chronic noncancer pain: A new Canadian practice guideline. CMAJ 2010;182(9):923–30.

76 Passik SD, Kirsh KL, Casper D. Addiction-related assessment tools and pain management: Instruments for Screening, treatment planning, and monitoring compliance. Pain Med 2008;9:S145–66.

77 Beletsky L, Rich JD, Walley AY. Prevention of fatal opioid overdose. JAMA 2012;308(18):1863–4.

78 Wheeler E, Davidson PJ, Jones TS, Irwin KS. Community-Based Opioid Overdose Prevention Programs Providing Naloxone—United States, 2010. Atlanta, Ga: Centers for Disease Control and Prevention; 2012.

79 Kim D, Irwin KS, Khoshnood K. Expanded access to naloxone: Options for critical response to the epidemic of opioid overdose mortality. Am J Public Health 2009;99(3):402–7.

80 American Medical Association. AMA Adopts New Policies at Annual Meeting: American Medical Association. 2012. Available at: https://www.ama-assn.org/ama/pub/news/news/2012-06-19-ama-adopts-new-policies.page (accessed December 2013).

Appendices

Appendix I

Prescription opioid drug products

Active Ingredient(s) by Generic Name
Alfentanil hydrochloride
Buprenorphine
Butorphanol tartrate
Codeine, acetaminophen
Codeine base
Codeine phosphate
Codeine phosphate, triprolidine, pseudoephedrine hydrochloride
Codeine phosphate, chlorpheniramine maleate
Codeine phosphate, guaifenesin, pseudophedrine
Codeine phosphate, pyrilamine maleate
Codeine phosphate, acetaminophen, gamma-aminobutyric acid
Codeine phosphate, brompheniramine maleate, pseudoephedrine hydrochloride
Codeine phosphate, brompheniramine maleate, phenylephrine hydrochloride
Codeine phosphate, butalbital, acetaminophen, caffeine
Codeine phosphate, butalbital, aspirin, caffeine
Codeine phosphate, carisoprodol, aspirin

Appendix I Continued

Active Ingredient(s) by Generic Name
Codeine phosphate, chlorcyclizine hydrochloride
Codeine phosphate, dexbrompheniramine maleate, pseudoephedrine hydrochloride
Codeine phosphate, guaifenesin, pseudoephedrine hydrochloride
Codeine phosphate, phenylephrine hydrochloride
Codeine phosphate, phenylephrine hydrochloride, diphenhydramine hydrochloride
Codeine phosphate, phenylephrine hydrochloride, chlorcyclizine hydrochloride
Codeine phosphate, phenylephrine hydrochloride, chlorpheniramine maleate
Codeine phosphate, phenylephrine hydrochloride, pyrilamine maleate
Codeine phosphate, promethazine hydrochloride
Codeine phosphate, promethazine hydrochloride, phenylephrine hydrochloride
Codeine phosphate, pseudoephedrine hydrochloride, chlorcyclizine HCl
Codeine phosphate, pseudoephedrine hydrochloride, chlorpheniramine maleate
Codeine phosphate, pseudoephedrine hydrochloride
Codeine phosphate, pseudoephedrine hydrochloride, pyrilamine maleate
Codeine sulfate
Dihydrocodeine bitartrate, acetaminophen, caffeine
Dihydrocodeine bitartrate, brompheniramine maleate, phenylephrine hydrochloride
Dihydrocodeine bitartrate, brompheniramine maleate, pseudoephedrine hydrochloride
Dihydrocodeine bitartrate, guaifenesin
Dihydrocodeine bitartrate, phenylephrine hydrochloride, guaifenesin
Dihydrocodeine bitartrate, phenylephrine hydrochloride, pyrilamine maleate
Fentanyl
Fentanyl citrate, bupivacaine HCl
Hydrocodone bitartrate, acetaminophen
Hydrocodone bitartrate, homatropine methylbromide
Hydrocodone bitartrate, ibuprofen
Hydrocodone bitartrate, chlorpheniramine maleate, pseudoephedrine hydrochloride
Hydrocodone bitartrate, pseudoephedrine hydrochloride
Hydrocodone polistirex, chlorpheniramine polistirex
Hydrocodone, acetaminophen, gamma-aminobutyric acid
Hydromorphone hydrochloride
Levorphanol tartrate
Meperidine hydrochloride
Methadone hydrochloride
Morphine
Nalbuphine hydrochloride
Naloxone, buprenorphine
Oxycodone, acetaminophen
Oxycodone, aspirin
Oxycodone hydrochloride
Oxycodone hydrochloride, ibuprofen
Oxymorphone hydrochloride
Pentazocine hydrochloride, acetaminophen
Pentazocine hydrochloride, naloxone hydrochloride
Pentazocine lactate
Propoxyphene hydrochloride
Propoxyphene hydrochloride, acetaminophen
Propoxyphene napsylate
Propoxyphene napsylate, acetaminophen
Sufentanil citrate
Tapentadol
Tramadol hydrochloride
Tramadol hydrochloride, acetaminophen
Tramadol hydrochloride, gamma-aminobutyric acid
Tramadol hydrochloride, acetaminophen

Appendix II

Logistic regression results: serious opioid-related toxicity or overdose

Covariate[†]	Odds Ratio	95% CI		*P*
Age group (years)				
18–34	*Reference*			
35–44	0.9	0.5	1.8	0.826
45–54	1.4	0.8	2.4	0.224
55–64	1.9	1.1	3.3	0.014
65+	1.8	1.1	3.2	0.028
Male	0.9	0.6	1.3	0.553
Race				
Non-Hispanic black	*Reference*			
Non-Hispanic white	1.8	1.3	2.4	<0.001
Hispanic	1.4	0.8	2.4	0.248
Other	1.6	1.1	2.2	0.013
Marital status				
Married (reference)	*Reference*			
Separated/divorced	1.1	0.9	1.4	0.404
Never married	1.4	1.0	1.8	0.044
Widowed	2.0	1.4	3.0	<0.001
Geographic region				
Northeast (reference)	*Reference*			
North central	1.3	0.9	1.8	0.184
South	1.2	0.9	1.7	0.316
West	1.8	1.3	2.5	0.001
Other	0.7	0.4	1.2	0.154
Comorbidity				
Individual CCI comorbidities				
Myocardial infarction	0.8	0.4	1.4	0.345
Congestive heart failure	1.1	0.7	1.8	0.674
Peripheral vascular disease	1.1	0.8	1.7	0.502
Cerebrovascular disease	0.7	0.4	1.1	0.132
Dementia	1.0	0.3	3.1	0.977
Chronic pulmonary disease	1.5	1.2	1.9	<0.001
Rheumatologic disease	0.3	0.1	0.9	0.027
Peptic ulcer disease	0.5	0.2	1.2	0.123
Mild liver disease	1.6	0.9	3.2	0.137
Diabetes	1.1	0.9	1.4	0.418
Hypertension	1.0	0.8	1.3	0.791
Depression	1.2	1.0	1.5	0.105
Use of warfarin	1.4	1.0	2.0	0.040
Hemiplegia or paraplegia	0.9	0.4	2.3	0.867
Renal disease	1.7	1.3	2.4	0.001
Any malignancy, including leukemia and lymphoma	1.3	1.0	1.7	0.086
Diabetes with chronic complications	1.0	0.7	1.4	0.769
Skin ulcers	2.4	1.5	3.8	<0.001
Moderate or severe liver disease	2.7	1.1	6.7	0.036
Metastatic solid tumor	2.3	1.3	4.0	0.007
HIV/AIDS	2.0	0.8	4.8	0.120
Other Selected comorbidities				
Nonpain related				
Substance abuse and nonopioid substance dependence	1.4	1.0	1.8	0.031
Opioid dependence	3.9	2.6	5.8	<0.001
Viral hepatitis	1.4	0.9	2.0	0.098
Alcoholic hepatitis	0.7	0.1	10.9	0.823
Pancreatitis	2.2	1.1	4.5	0.032
Sexually transmitted disease	1.4	0.6	3.1	0.458
Herpes simplex infection	0.8	0.3	2.2	0.639
Skin infections/abscesses	0.5	0.3	0.9	0.010
Sleep apnea	1.3	1.0	1.8	0.040
Tobacco use disorder	1.2	1.0	1.5	0.066
PTSD	1.0	0.8	1.3	0.985
Bipolar disorder	1.7	1.2	2.4	0.005

Appendix II Continued

Covariate†	Odds Ratio	95% CI		P
ADHD	0.3	0.1	1.0	0.048
Schizophrenia	1.6	0.9	2.8	0.105
Anxiety disorder	1.1	0.9	1.5	0.384
OCD	0.6	0.1	2.8	0.552
Cardiovascular disease	1.3	0.8	2.0	0.243
Obesity	1.1	0.8	1.4	0.498
Pain related				
Low back disorders	1.1	0.9	1.4	0.241
Other back/neck disorders	1.1	0.9	1.4	0.309
Neuropathic disorders	1.0	0.8	1.3	0.815
Fibromyalgia	1.2	0.7	2.0	0.574
Headache/migraine	1.2	0.8	1.7	0.322
Burns	0.8	0.2	3.8	0.758
Traumatic injury	1.6	1.3	2.0	<0.001
Motor vehicle accidents	2.4	0.7	7.6	0.145
Prescription drug use				
Opioids				
By active ingredient				
Hydrocodone	1.0	0.8	1.4	0.779
Oxycodone	1.4	1.1	1.9	0.017
Tramadol	0.7	0.5	1.0	0.043
Codeine	1.3	0.9	1.9	0.146
Fentanyl	0.8	0.1	6.9	0.813
Morphine	1.6	1.0	2.5	0.079
Hydromorphone	2.4	1.2	4.7	0.012
Methadone	1.6	1.0	2.7	0.079
Oxymorphone	0.3	0.0	5.4	0.377
Other*	1.7	0.1	52.5	0.775
By formulation				
Short acting	*Reference*			
ER/LA	1.9	1.1	3.2	0.018
By route				
Oral	*Reference*			
Parenteral or transdermal	2.3	0.3	18.7	0.433
Number of opioid prescriptions dispensed, mean (SD)	1.0	1.0	1.0	0.852
Number of unique opioid NDCs, mean (SD)	1.0	0.9	1.1	0.488
Maximum prescribed daily morphine equivalent dose (MED, mg/day)				
1–<20 (reference)	*Reference*			
20–<50	1.5	1.1	1.9	0.011
50–<100	2.2	1.5	3.2	<0.001
≥100	4.1	2.6	6.5	<0.001
Nonopioid drugs of interest				
Benzodiazepines	1.4	1.1	1.7	0.004
Antidepressants	1.6	1.3	2.0	<0.001
Nonopioid analgesics	0.9	0.7	1.2	0.557
Muscle relaxants	1.1	0.9	1.4	0.293
Other sedatives	1.1	0.8	1.5	0.521
Antipsychotics	1.3	1.0	1.7	0.045
Stimulants	1.9	0.8	4.6	0.179
All-cause health care utilization during the preceding 6 months				
Days of hospitalization				
0	*Reference*			
≥1	2.9	2.3	3.6	<0.001

* Other opioids included meperidine and pentazocine/naloxone. Methadone is a long-acting opioid.

ADHD = attention deficit hyperactivity disorder; CCI = Charlson Comorbidity Index; CI = confidence interval; ER/LA = extended release or long acting; MED = morphine equivalent dose; NDC = National drug code; OCD = obsessive–compulsive disorder; PTSD = post-traumatic stress disorder; SD = standard deviation.

†Covariates with frequencies less than 10 or which prevented model convergence were not included in the full model.

EXHIBIT G

STATE OF TEXAS

COUNTY OF NEWTON

Consider and take action to approve Resolution for approval of bringing suit on behalf of Newton County, Texas, vs. various drug manufacturers, developers, suppliers and others of a class of pharmaceutical class of drugs commonly referred to as opioids and approval of Professional Services Agreement for Special Counsel.

WHEREAS, it reasonably appears from public information that there exists in Newton County an epidemic of opioid drug abuse created and/or fueled by misconduct of opioid manufacturers and distributors in their improper promotion and over-supply of those drugs, thus creating a public nuisance within Newton County; and

WHEREAS, Newton County is empowered by law to seek recompense for its expenditures to combat public nuisance; and

WHEREAS, enforcement of the law regarding public nuisance requires Newton County to institute civil legal proceedings requiring legal services, and the Newton County Commissioners Court finds as follows:

(1) there is a substantial need for the legal services;

(2) the legal services cannot be adequately performed by the attorneys and supporting personnel of Newton County or by the attorneys and supporting personnel of another governmental entity; and

(3) the legal services cannot reasonably be obtained from attorneys in private practice under a contract providing only for the payment of hourly fees, without regard to the outcome of the matter, because of the nature of the matter for which the services will be obtained and because Newton County does not have appropriated funds available to pay the estimated amounts required under a contract providing only for the payment of hourly fees; and

WHEREAS, Newton County is empowered to employ Special Counsel to prosecute lawful reimbursement of monies spent by Newton County to combat the opioid epidemic in Newton County and has selected the legal team of Simon Greenstone Panatier Bartlett, P.C. and Paul D. Henderson, P.C. and Dies & Parkhurst, L.L.P. to serve as Special Counsel.

THEREFORE, BE IT HEREBY RESOLVED that:

1. The Commissioner's Court approves Resolution to bring suit on behalf of Newton County, Texas, versus various drug manufacturers, developers, suppliers and others of a class of

pharmaceutical class of drugs commonly referred to as opioids and approval of Professional Services Agreement for Special Counsel.

2. The Commissioners Court selects the legal team of Simon Greenstone Panatier Bartlett, P.C. and Paul D. Henderson, P.C. and Dies & Parkhurst, L.L.P. to serve as Special Counsel and approves and adopts the terms and conditions of employment of such counsel as set out in the attached Professional Services Agreement. Special Counsel will work under the oversight and approval of the Newton County District Attorney or her designee.

3. The Commissioners Court authorizes the District Attorney or her designee and Special Counsel to file such claims and litigation as Special Counsel deems necessary against various drug manufacturers, developers, suppliers and others of a class of pharmaceutical class of drugs commonly referred to as opioids

4. The Newton County Judge or his designee is authorized to execute on behalf of Newton County an agreement with Special Counsel (hereinafter the "Agreement") containing terms and provisions substantially similar to those contained in the attached agreement because the Court finds that there is a substantial need for the legal services of Special Counsel which cannot adequately be performed by attorneys and supporting personnel of Newton County or another public agency, nor can the legal services reasonably be obtained from attorneys in private practice under a contract providing only for payment of hourly fees without regard to the outcome of the matter because of the nature of the representation.

5. All fees to be paid to Special Counsel are contingent upon the recovery of the penalties, attorneys' fees and costs as provided for in the Agreement and shall be paid only from such recovery and no money shall be due or paid from the General Fund or any special fund under the Agreement.

6. All Newton County officials and employees are authorized to do any and all things necessary or convenient to accomplish the purposes of this order.

THIS RESOLUTION WAS ADOPTED this 9th day of July, 2018, by Commissioners' Court of Newton County, Texas.

Paul Pace
County Judge

Attested: Sandra K. Duckworth
County Clerk

EXHIBIT H

RETENTION AGREEMENT

WHEREAS, Newton County has determined that claims should be made against Purdue Pharma, L.P., Purdue Pharma, Inc., The Purdue Frederick Company, Inc., Teva Pharmaceutical Industries USA, Ltd., Cephalon, Inc., Johnson & Johnson, Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica, Inc. n/k/a Janssen Pharmaceuticals, Inc., Ortho-McNeil-Janssen Pharmaceuticals, Inc. n/k/a Janssen Pharmaceuticals, Inc., Endo Health Solutions Inc., Endo Pharmaceuticals, Inc., Allergen, PLC f/k/a Actavis, PLC, Actavis, Inc. f/k/a Watson Pharmaceuticals, Inc., Watson Laboratories, Inc., Actavis, LLC, and Actavis Pharma, Inc. f/k/a Watson Pharma, Inc., McKesson Corporation, AmerisourceBergen Corporation, and any other entities which have engaged in violations of the Texas Controlled Substances Act and other violations of law in the fraudulent marketing and sales of certain highly addictive, opiate-derived painkillers for purposes for which they are neither safe nor effective; and

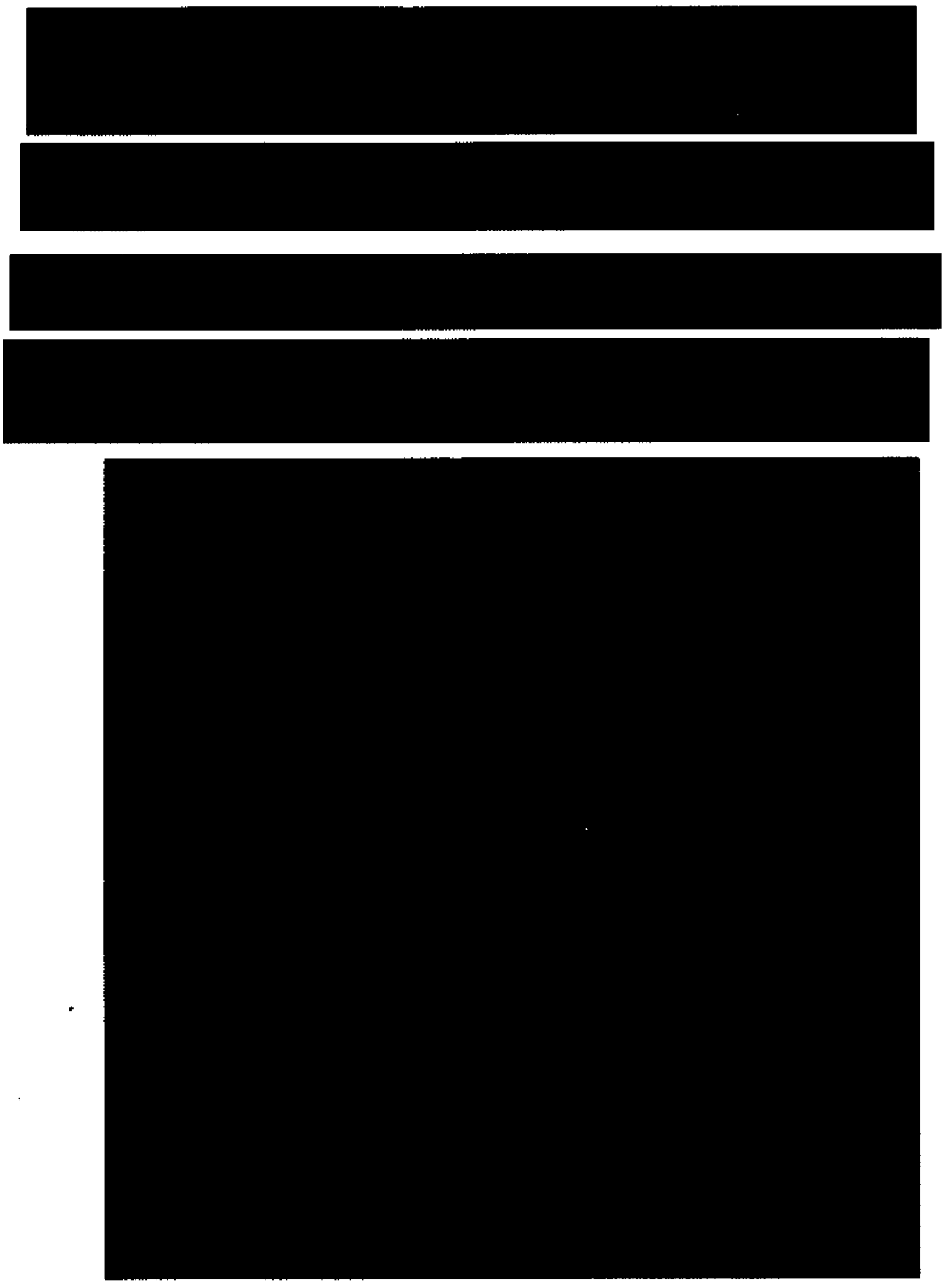
[redacted]

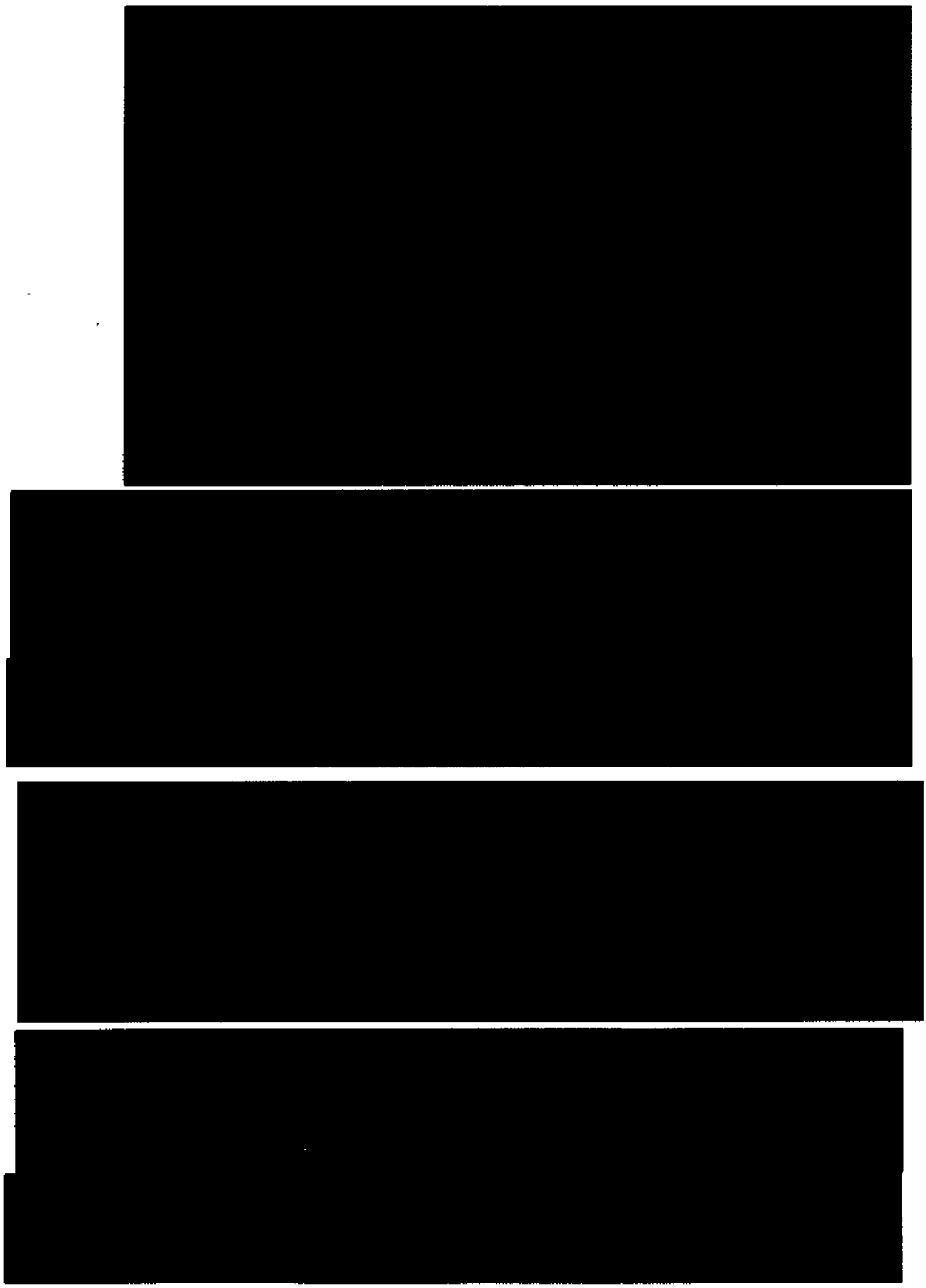
WHEREAS, Newton County has further determined that it is in the best interests of the County and its citizens that the County retain attorneys with significant litigation experience; and

WHEREAS, Simon Greenstone Panatier, P.C. Paul D. Henderson, P.C. and Dies & Parkhurst, L.L.P. are experienced at such litigation and consented to represent Newton County respecting the claims and pursuant to the terms and conditions hereof.

IT IS, ACCORDINGLY, AGREED as follows:

[redacted]





DATED this the 7th day of JULY, 2018.

NEWTON COUNTY

BY: _____
Paul Price, Newton County Judge

SIMON GREENSTONE PANATIER, P.C.

BY: _____
Jeffrey Simon, Shareholder

PAUL D. HENDERSON, P.C.

BY: _____
Paul Henderson, Shareholder

DIES & PARKHURST, L.L.P.

BY: _____
David Dies, Shareholder

APPROVED BY:

OFFICE OF THE TEXAS COMPTROLLER OF PUBLIC ACCOUNTS:

_____ Date: 8·9·18
By: Deputy Comptroller or his/her designee